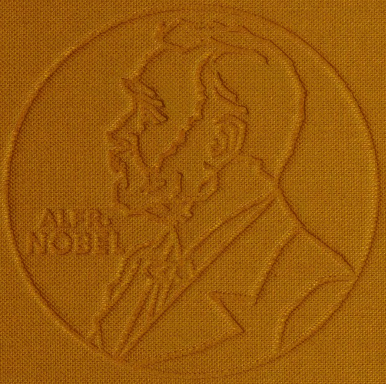
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Foreword

The Nobel Foundation has, by agreement, granted the Elsevier Publishing Company of Amsterdam the right to publish in English language the Nobel Lectures for 1901–1962. The lectures in the five Nobel Prize domains: Physics, Chemistry, Physiology or Medicine, Literature, and Peace will appear separately, according to the subject. The scientific lectures will each cover three volumes and those in literature and peace one volume each. Short biographical notes and the presentation speeches will also be included.

The Nobel Foundation has since 1901 each year published *Les Prix Nobel* which contains all Nobel Lectures of that year, always in the language in which they were given, as well as short biographies of the laureates. In addition an account is given of the prize-award ceremonies in Stockholm and in Oslo, including presentation addresses and after-dinner speeches, etc., thus covering the whole field of Nobel Prize events of one particular year.

In the Elsevier series the Nobel Lectures, presentation addresses, and biographies will now be more readily accessible to those who wish to follow the development in only certain of the Nobel subjects, as reflected in the prize awards during the years passed. For practical reasons English has been chosen as common language for this series.

It is the hope of the Nobel Foundation that the volumes to be published by Elsevier Publishing Company will supplement *Les Prix Nobel* and that together they will serve to spread knowledge of those landmarks on the road of human progress that have been honoured by Nobel Prizes.

Arne Tiselius – President, Nobel Foundation

Publisher's Note

During the realization of this work we have been confronted by many problems. In solving the great majority of them we have relied heavily upon assistance, both invited and spontaneously offered, from many quarters.

To some problems there was no solution to be found; in particular, it proved impossible to obtain, for some of the lectures, the original photographs or blocks used for the illustrations. As an inevitable consequence of this it was found necessary to reproduce these illustrations from a printed original; this naturally renders them less perfect than we would have wished. We thank those who were able to lend us original material.

The translations of those lectures which were delivered in a language other than English were prepared by the Babylon Translation Service, London. We are indebted to Mr. D. F. Styles, Mr. M. Fedorski (both of Manchester), and Dr. G. Lapage of Cambridge, for research on, and preparation of, most of the biographies. Completion of these, and the addition of much detail, was achieved with the cooperation of many laureates themselves, their colleagues and assistants, and other individuals whose help was requested. To all of them we would like to offer our sincerest thanks in appreciation of their efforts.

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Chemistry 1922

FRANCIS WILLIAM ASTON

«for his discovery, by means of his mass spectrograph, of isotopes in a large number of non-radioactive elements, and for his enunciation of the whole-number rule»

Chemistry 1922

Presentation Speech by Professor H. G. Söderbaum, member of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

As we have just seen, the conception of isotopy has mainly developed out of our knowledge of the radioactive elements, their coming into existence, their transformation, and their other relations. Now the obvious thought presented itself that *non*-radioactive elements – which, of course, include the majority of our commonest elements – might also in the same way consist of mixtures of isotopes which were inseparable by chemical methods. But it was not easy to demonstrate such a state of things. The radioactive phenomena, which had hitherto formed the guiding star of research, here refused to render service any longer. It was necessary to fall back exclusively on a careful study of such physical properties as could be conceived as being affected, to a greater or lesser extent, by the *mass* of the atom.

The first attempts in this direction were carried out by the well-known Nobel Prize laureate, Sir J. J. Thomson. In this work he made use of the so-called anode rays, that is to say the positively charged particles of gas which in a vacuum-tube are hurled at a high speed against the negative electrode. If one causes them to pass through an aperture in this electrode and then to be acted upon by an electric and a magnetic field, they are deflected, and the extent of the deflection is determined by the ratio of mass to charge. By measuring this deviation, it should be possible to obtain a measure of the mass of the particles appearing in the rarefied gas and consequently also one should be able to demonstrate the existence of isotopes, inasmuch as these must be characterized by different values of the mass, or in other words, by different atomic weights.

Thomson's experiments had not yet led to any decisive result when the outbreak of the World War led to an interruption in the work for several years. In 1919 that work was taken up again by Thomson's former pupil, Dr. Aston of Cambridge. He now constructed an apparatus, known as the mass spectrograph, which, though in the main founded on the same principles as Thomson's, yet, in comparison with that, exhibits certain very substantial improvements, calculated to lead to results many times more precise.

This is not the place to enter into the extremely involved design of that instrument, which is as ingenious as it is exact. Suffice it to say that the rays which have a constant ratio between electrical charge and mass are focussed, that is to say caused to converge to a common centre, the situation of which, in relation to other similar focusses, can be exactly determined with the help of a photographic plate. By this means there is attained what is known as a mass spectrogram, that is to say a series of lines in which each line corresponds to a certain atomic weight, and where the numerical value of each atomic weight can be read off from the distance of the line from the line or lines which are produced by any fundamental substance that is chosen as a standard – usually carbon-12 or oxygen-16. The degree of exactitude by which the atomic weights can thus be determined by the mass spectrograph amounts, in favourable cases, to one in a thousand.

Thanks to the substantially increased sharpness and fineness that the analysis of the anode rays has obtained by means of the mass spectrograph, Aston has succeeded in proving that a large number of fundamental elements which have hitherto been regarded as simple are in reality complexes of two or more isotopes. This is the case, within the group of the inactive gases, with neon, krypton, and xenon; within the halogen group, with chlorine and bromine; within the alkali metals, with lithium, potassium, and rubidium; further complexes are boron and silicon, tin and selenium, calcium and mercury, etc. On the other hand, helium, fluorine and iodine, carbon and oxygen, nitrogen, phosphorus and arsenic, sodium and caesium, etc. have been found to possess clear criteria of unity.

This result is in itself extremely remarkable, and, as can easily be seen, it is of fundamental importance for the whole of chemical science; but this is not the most remarkable of the results which have been obtained with the mass spectrograph. It is indeed still more remarkable that all the masses so far measured of the recently enumerated elements and several others, and also the masses of their isotopes, can be expressed by means of whole numbers in relation to oxygen-16. As the number of fundamental substances investigated amounts to over 30, and as the number of demonstrated isotopes rather exceeds than falls short of 50, this accordance can scarcely be regarded as merely fortuitous, but must be regarded as the expression of a natural law of general validity. It has indeed been named the *whole-number rule*.

By this discovery a riddle which for over a hundred years has engaged chemical research has attained its solution, and a surmise which for thousands of years has floated before the human mind has thereby been confirmed.

Long ago, in certain philosophers of ancient Hellas, we find assertions of the unity of matter, of a primitive substance which is common to all substances.

An obscure notion in the same direction undoubtedly floated before the minds of the alchemists of the Middle Ages and of the Renaissance in their incessant endeavours to transmute one metal into another.

The thought was developed more clearly in the seventeenth century by Robert Boyle; according to him, all bodies consist of one and the same primitive material; their varying multiplicity is due to the different size and shape of the small parts or corpuscles, to their different states of rest or movement.

But this way of looking at things did not become of burning importance to scientific chemical research until 1815, when the English physician Prout put forward his hypothesis that the atoms of the elements are all made up of aggregations of a larger or smaller number of atoms of the lightest known element, hydrogen.

If this view were correct, evidently the atomic weights of all elements ought to be exact multiples of that of hydrogen.

So far, however, experience has spoken another language. The greatest masters of chemical science in the sphere of precise determinations – a Berzelius, a Stas, and in our own days a Richards – have one after another established the existence of one and the same state of things, namely that, though the atomic weights of some elements are very nearly whole number multiples of that of hydrogen, yet on the other hand others defy the most persistent efforts to eliminate their inherent fractions, which far exceed the limits of errors of observation. Prout's hypothesis, therefore, was regarded as disproved more and more definitely as the determinations of atomic weights became worked out with a greater degree of perfection and seemed to yield results incompatible with the hypothesis.

Through Aston's discoveries this theory has now been restored to life in a trice, although, it is true, in a form different from that which its originator imagined, inasmuch as, at the present standpoint of science, the simplest small parts of matter must be conceived as consisting of two essentially different kinds, namely of positively and negatively charged small particles – protons and electrons.

The broken numbers in the atomic weights of certain fundamental substances, in fact, now appear simply as statistical effects of the internal quantitative relations of their isotopic constituents.

A typical example of an element with such a broken atomic weight is

offered by chlorine. Its atomic weight, according to the most exact determinations, is 35.46. Aston now shows that what we have hitherto called chlorine is a mixture of at least two isotopic elements, one with the atomic weight of 35, the other with the atomic weight of 37, combined with one another in such relations that the weight of the mixture is exactly 35.46.

One element, however, forms an exception from the whole-number rule, and this exception is no less interesting than the law itself. It is precisely the atomic weight of hydrogen which has in the mass spectrograph shown itself to be encumbered with a fraction; not large, it is true – it amounts to only 0.008 – but still sufficiently large not to be explained away as an error of observation. The atomic weight of hydrogen has thus been found to be noticeably heavier than the unity which holds good with regard to the other elements in relation to oxygen-16.

But also according to Rutherford's nucleus theory hydrogen assumes a special position in relation to all other elements. Its atom, indeed, is the only one of which the nucleus is not composed of a number of tightly packed mass units, but consists of one single positive particle of electricity, proton. In view of this fact the divergence of hydrogen from the whole-number rule cannot be said to be entirely unexpected, least of all if one adopts the view that the gulf between mass and energy is less insuperable than had been previously supposed.

Doctor Aston. The Royal Swedish Academy of Sciences has resolved to award you this year's Nobel Prize in Chemistry for your discovery, made with the help of the mass spectrograph, of the isotopes of a great number of inactive elements and of the whole-number rule, discoveries which are of fundamental importance for the study of nature in general and for chemical science in particular. While expressing a cordial hope that it may be vouchsafed to you in the future to add further scientific successes to those which you have already obtained, I have the honour to convey to you the congratulations of the Academy on the distinction the outward and visible signs of which you are now about to receive.

Francis W. Aston

Mass spectra and isotopes

Nobel Lecture, December 12, 1922

Dalton's statement of the Atomic Theory, which has been of such incalculable value in the development of chemistry, contained the postulate that « atoms of the same element are similar to one another, and equal in weight ». The second part of this postulate cannot, in general, be tested by chemical methods, for numerical ratios are only to be obtained in such methods by the use of quantities of the element containing countless myriads of atoms. At the same time it is somewhat surprising, when we consider the complete absence of positive evidence in its support, that no theoretical doubts were publicly expressed until late in the nineteenth century.

There are two methods by which the postulate can be tested experimentally, either by comparing the weights of the individual atoms, or alternatively by demonstrating that samples of an element can exist which though chemically identical yet have different atomic weights. The latter method, by which the existence of *isotopes* was first proved, has been fully dealt with in the previous lecture by Professor Soddy. The more direct method, with which this lecture is concerned, can be applied by means of the analysis of positive rays.

The condition for the development of these rays is briefly ionization at low pressure in a strong electric field. Ionization, which may be due to collisions or radiation, means in its simplest case the detachment of one electron from a neutral atom. The two resulting fragments carry charges of electricity of equal quantity but of opposite sign. The negatively charged one is the electron, the atomic unit of negative electricity itself, and is the same whatever the atom ionized. It is extremely light and therefore in the strong electric field rapidly attains a high velocity and becomes a cathode ray. The remaining fragment is clearly dependent on the nature of the atom ionized. It is immensely more massive than the electron, for the mass of the lightest atom, that of hydrogen, is about 1,850 times that of the electron, and so will attain a much lower velocity under the action of the electric field. However, if the field is strong and the pressure so low that it does not collide with other atoms too frequently, it will ultimately attain a high speed in a direction

opposite to that of the detached electron, and become a «positive ray». The simplest form of positive ray is therefore an atom of matter carrying a positive charge and endowed, as a result of falling through a high potential, with sufficient energy to make its presence detectable. Positive rays can be formed from molecules as well as atoms, so that it will at once be seen that any measurement of their mass will give us direct information as to the masses of atoms of elements and molecules of compounds, and that this information will refer to the atoms or molecules *individually*, not, as in chemistry, to the mean of an immense aggregate. It is on this account that the accurate analysis of positive rays is of such importance.

In the *parabola* method of analysis devised by Sir J. J. Thomson, the rays generated by means of an electric discharge, after reaching the surface of the cathode, enter a long and very fine metal tube. By this means a narrow beam of rays is produced which is subjected to deflection by electric and magnetic fields, and finally falls upon a screen of fluorescent material or a photographic plate. The fields are arranged so that the two deflections are at right angles to each other. If we call the displacement on the plate due to the electric field x and that due to the magnetic field y for any particle, (x, y) will be the rectangular coordinates of the point where it strikes the plate. Simple dynamics show that if the angle of deflection is small, for a particle of mass m, charge e and velocity v, the electric deflection $x = k(Xe/mv^2)$ and the magnetic deflection $y = k'(He/mv)$ where X and H are the magnetic and electric fields, and k and k' constants depending solely on the dimensions and form of the apparatus. Hence if both fields are on together, the locus of impact of all particles of the same e/m but varying velocity will be a parabola. Since e must be the electronic charge, or a simple multiple of it, measurement of the relative positions of the parabolas on the plate enables us to calculate the relative masses of the particles producing them, that is, the masses of the individual atoms. The fact that the streaks were definite, sharp parabolas, and not mere blurs, constituted the first direct proof that atoms of the same element were, even approximately, of equal mass.

Many gases were examined by this method and some remarkable compounds, such as H_3, discovered by its means. When in 1912 neon was introduced into the discharge tube, it was observed to exhibit an interesting peculiarity. This was that whereas all elements previously examined gave single, or apparently single, parabolas, that given by neon was definitely double. The brighter curve corresponded roughly to an atomic weight of 20, the fainter companion to one of 22, the atomic weight of neon being

20.20. In consequence of reasoning adduced from the characteristics of the line 22, Sir J. J. Thomson was of the opinion that it could not be attributed to any compound, and that therefore it represented a hitherto unknown elementary constituent of neon. There was no room for such an element in the Periodic Table; but the suggestion that atoms of different weight could exist having identical chemical properties had just been promulgated, and the facts could be explained very well by the supposition that neon was a mixture of two such bodies. I therefore undertook to investigate this point as fully as possible.

The first line of attack was an attempt at separation by fractional distillation over charcoal cooled with liquid air, but even after many thousands of operations the result was entirely negative. The density of the fractions was determined by means of a special quartz microbalance and was found to agree in every case with the accepted atomic weight of 20.20 to an accuracy of 1 in 1000.

The second method I employed was that of fractional diffusion through pipeclay, which after months of arduous work gave a small but definite positive indication of separation. A difference of about 0.7 per cent between the densities of the heaviest and lightest fractions was obtained. If V is the initial and v the residual volume of gas, Rayleigh's theory of diffusion gives an enrichment of approximately $(V/v)^{1/21}$ in respect to the heavier constituent in the residue in the case of neon. This is the result of a single operation, and the effective ratio V/v can be increased indefinitely by repeated operations – in these experiments it amounted to several thousand – but from the nature of the work cannot be stated exactly. If, to be perfectly safe, we take V/v as between 500 and 10,000, the theoretical increase in density of the heaviest fraction over normal should lie between 0.34 and 0.55 per cent. It was actually 0.4, quite a reasonable figure considering the inefficiency of the method. The decrease in density in the lightest fraction was rather less owing to the loss of a portion of the gas during the experiment. When the war interrupted the research, it might be said that several independent lines of reasoning pointed to the conclusion that neon was a mixture of isotopes, but none of these could be said to carry absolute conviction.

By the time the work was resumed in 1919 the existence of isotopes among the products of radioactivity had been put beyond all reasonable doubt by the work on the atomic weight of lead and was accepted generally. This fact automatically increased both the value of the evidence of the complex nature of neon and the urgency of its definite confirmation. It was realized that

separation could only be very partial at the best, and that the most satisfactory proof would be afforded by measurements of atomic weight by the method of positive rays. These would have to be so accurate as to prove beyond dispute that the accepted atomic weight lay between the real atomic weights of the constituents, but corresponded with neither of them.

The parabola method was not capable of this, for the measurements obtained by means of the best apparatus so far constructed were only reliable to about one per cent. I therefore started to examine systematically all possible alternative methods, particularly those in which the fine circular tube could be replaced by a pair of parallel slits. The reason for this is that the intensity of the beam of rays will only be reduced in proportion to the square of the breadth of the slits, whereas for the circular tube the reduction is proportional to the fourth power of its breadth.

It is clearly only possible to use slits satisfactorily if the electric and magnetic deflections are both in the same plane at right angles to the slits, and during a mathematical investigation originally started to determine the most favourable positions of the slits, fields, and plate, I was fortunate enough to hit on the focussing principle used in the mass spectrograph. A diagram of this apparatus is given in Fig. 1. The exact mathematical analysis of the principle has now been worked out, but it will be enough to give the approximate theory here.

The rays after arriving at the cathode face pass through two very narrow parallel slits of special construction S_1S_2, and the resulting thin ribbon is spread out into an electric spectrum by means of the parallel plates P_1P_2.

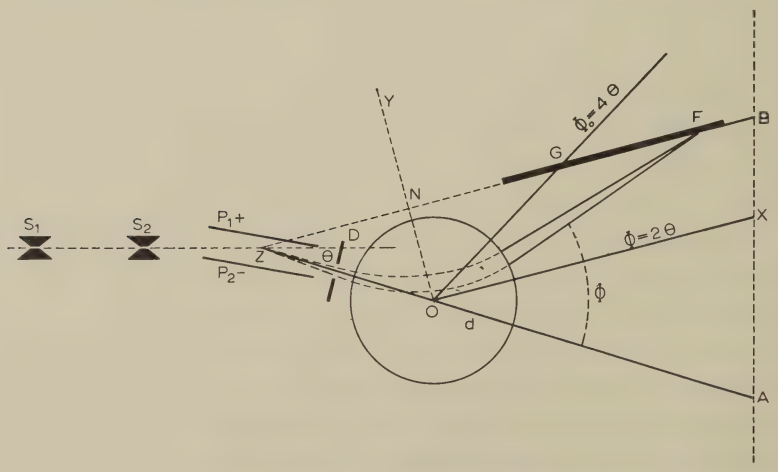


Fig. 1. Diagram of mass spectrograph.

After emerging from the electric field the rays may be taken, to a first order of approximation, as radiating from a virtual source Z half-way through the field on the line S_1S_2. A group of these rays is now selected by means of the diaphragm D, and allowed to pass between the parallel poles of a magnet. For simplicity the poles are taken as circular, the field between them uniform and of such sign as to bend the rays in the opposite direction to the foregoing electric field.

If θ and φ be the angles (taken algebraically) through which the selected beam of rays is bent by passing through fields of strength X and H, then

$$\theta v^2 = lX\frac{e}{m} \qquad (1)$$

and

$$\varphi v = LH\frac{e}{m} \qquad (2)$$

where l, L are the lengths of the paths of the rays in the fields. Eq. (1) is only true for small angles, but exact enough for practice. It follows that over the small range of θ selected by the diaphragm, θv^2 and φv are constant for all rays of given e/m, therefore

$$\frac{\delta\theta}{\theta} + \frac{2\delta v}{v} = 0, \quad \text{and} \quad \frac{\delta\varphi}{\varphi} + \frac{\delta v}{\varphi} = 0, \quad \text{so that} \quad \frac{\delta\theta}{\theta} = \frac{2\partial\varphi}{\varphi}$$

when the velocity varies in a group of rays of given e/m. This equation appears correct within practical limits for large circular pole-pieces.

Referred to axes OX, OY the focus is at $r\cos(\varphi - 2\theta')$, $r\sin(\varphi - 2\theta')$, or r, $b.2\theta'$; so that to a first-order approximation, whatever the fields, so long as the position of the diaphragm is fixed, the foci will all lie on the straight line ZF drawn through Z parallel to OX. For purposes of construction, G the image of Z in OY is a convenient reference point, φ being here equal to $4\theta'$. It is clear that a photographic plate, indicated by the thick line, will be in fair focus for values of e/m over a range large enough for accurate comparison of masses.

Since it is a close analogue of the ordinary spectrograph and gives a «spectrum» depending upon mass alone, the instrument is called a «mass spectrograph» and the spectrum it produces a «mass spectrum».

Fig. 2 shows a number of typical mass spectra obtained by this means. The numbers above the lines indicate the masses they correspond to, on the

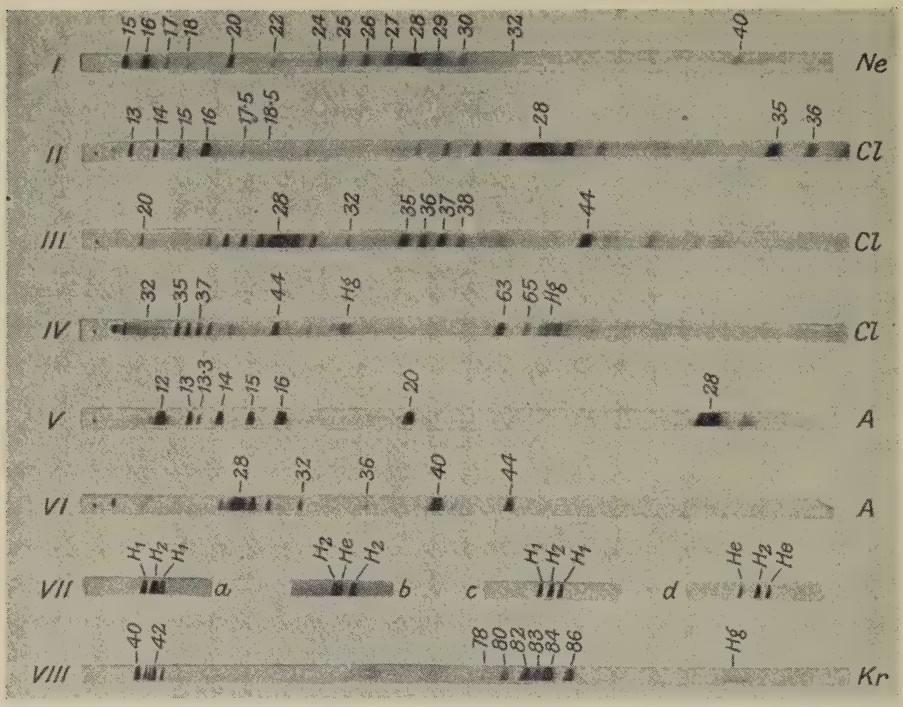


Fig. 2. Typical mass spectra.

scale O = 16. It will be noticed that the displacement to the right with increasing mass is roughly linear. The measurements of mass made are not absolute, but relative to lines which correspond to known masses. Such lines due to hydrogen, carbon, oxygen, and their compounds are generally present as impurities or purposely added, for pure gases are not suitable for the smooth working of the discharge tube. The two principal groups of these reference lines are the C_1 group due to C (12), CH (13), CH_2 (14), CH_3 (15), CH_4 or O (16), and the C_2 group (24 to 30) containing the very strong line C_2H_4 or CO (28). These groups will be seen in several of the spectra reproduced, and they give, with the CO_2 line (44), a very good scale of reference.

It must be remembered that the ratio of mass to charge is the real quantity measured by the position of the lines. Many of the particles are capable of carrying more than one charge. A particle carrying two charges will appear as having half its real mass, one carrying three charges as if its mass was one-third, and so on. Lines due to these are called lines of the second and third order. Lines of high order are particularly valuable in extending our scale

of reference. When neon was introduced into the apparatus, four new lines made their appearance at 10, 11, 20, and 22. The first pair are second-order lines and are fainter than the other two. All four are well placed for direct comparison with the standard lines, and a series of consistent measurements showed that to within about one part in a thousand the atomic weights of the isotopes composing neon are 20 and 22 respectively. Ten per cent of the latter would bring the mean atomic weight to the accepted value of 20.20, and the relative intensity of the lines agrees well with this proportion. The isotopic constitution of neon was therefore settled beyond all doubt.

Spectrum I on the plate shows the first-order lines of neon and some of the reference lines with which they were compared.

The element chlorine was naturally the next to be analysed, and the explanation of its fractional atomic weight was obvious from the first plate taken. Its mass spectrum is characterized by four strong first-order lines at 35, 36, 37, 38. There is no sign whatever of any line at 35.46. The simplest explanation of the group is to suppose that the lines 35 and 37 are due to the isotopic chlorines, and lines 36 and 38 to their corresponding hydrochloric acids. The elementary nature of lines 35 and 37 is also indicated by the second-order lines at 17.5, 18.5, and also, when phosgene was used, by the appearance of lines at 63, 65, due to $CO^{35}Cl$ and $CO^{37}Cl$.

Later it was found possible to obtain the spectrum of negatively charged rays. These rays are formed by a normal positively charged ray picking up two electrons. On the negative spectrum of chlorine only two lines, 35 and 37, can be seen, so that the lines at 36 and 38 cannot be due to isotopes of the element. These results, taken with many others which cannot be stated here in detail, show that chlorine is a complex element, and that its isotopes are of atomic weight 35 and 37. Spectra II, III, and IV show the results with chlorine taken with different magnetic field strengths.

The mass spectrum of argon shows an exceedingly bright line at 40, with second-order line at 20, and third-order line at $13\frac{1}{3}$. The last is particularly well placed between known reference lines, and its measurement showed that the triply charged atom causing it, had a mass 40 very exactly. Now the accepted atomic weight of argon is less than 40, so the presence of a lighter isotope was suggested. This was found at 36, and has now been fully substantiated; its presence to the extent of about 3 per cent is sufficient to account for the mean atomic weight obtained by density determinations.

The elements hydrogen and helium present peculiar difficulties, since their lines are so far removed from the ordinary reference scale, but, as the lines

were expected to approximate to the terms of the geometrical progression 1, 2, 4, 8, etc., the higher terms of which are known, a special method was adopted by which a two-to-one relation could be tested with some exactness. Two sets of accumulators were selected, each giving very nearly the same potential of about 250 volts. The potentials were then made exactly equal by means of a subsidiary cell and a current-divider, the equality being tested to well within 1,000 by means of a null instrument. If exposures are made with such potentials applied to the electric plates first in parallel and then in series, the magnetic field being kept constant, all masses having an exact two-to-one relation will be brought into coincidence on the plate. Such coincidences cannot be detected on the same spectrum photographically; but if we first add and then subtract a small potential from one of the large potentials, two lines will be obtained which closely bracket the third. To take an actual instance—using a gas containing hydrogen and helium, with a constant current in the magnet of 0.2 ampere, three exposures were made with electric fields of 250, 500 + 12, and 500 − 12 volts, respectively. The hydrogen molecule line was found symmetrically bracketed by a pair of atomic lines (Spectrum VII, *a* and *c*), showing within experimental error that the mass of the molecule is exactly double the mass of the atom. When after a suitable increase of the magnetic field the same procedure was applied to the helium line and that of the hydrogen molecule, the bracket was no longer symmetrical (Spectrum VII, *b*), nor was it when the hydrogen molecule was bracketed by two helium lines (*d*). Both results show in an unmistakable manner that the mass of He is less than twice that of H_2. In the same way He was compared with O^{++} and H_3. The values obtained by its use can be checked in the ordinary way by comparing He with C^{++} and H_3 with He, these pairs being close enough together for the purpose. The following table gives the range of values obtained from the most reliable plates:

Line	*Method*	*Mass assumed*	*Mass deduced*
He	Bracket	$O^{++} = 8$	3.994–3.996
	Direct	$C^{++} = 6$	4.005–4.010
H_3	Bracket	$C^{++} = 6$	3.025–3.027
	Direct	He $= 4$	3.021–3.030
H_2	Bracket	He $= 4$	2.012–2.018

From these figures it is safe to conclude that hydrogen is a simple element and that its atomic weight, determined with such consistency and accuracy by chemical methods, is the true mass of its atom.

The heavy inert gases give interesting and complicated results. Krypton is characterized by a remarkable group of five strong lines at 80, 82, 83, 84, 86, and a faint sixth at 78. This cluster of isotopes is beautifully reproduced with the same relative values of intensity in the second, and fainter still in the third order. These multiply-charged clusters give most reliable values of mass, as the second order can be compared with A (40) and the third with CO or N_2 (28) with the highest accuracy. It will be noted that one member of each group is obliterated by the reference line, but not the same one. The singly and doubly charged krypton clusters can be seen to the right and left of Spectrum VIII. It will be noticed that krypton is the first element examined which shows unmistakable isotopes differing by one unit only.

Xenon is even more complex. It consists of five strong components 129, 131, 132, 134, 136 and two fainter ones 128, 130; in addition recent work has revealed two extremely faint probable ones 124, 126, making nine in all.

Mercury was early recognized to be a mixture of isotopes. Its components are however too close to be perfectly resolved by the present apparatus. Its first, second, third, and higher order lines appear as a series of characteristic groups around positions corresponding to masses 200, 100, $66\frac{2}{3}$, etc. Some of these will be easily distinguished on the spectra reproduced in the plate.

In addition to those mentioned above, the elements nitrogen, boron, fluorine, silicon, bromine, sulphur, phosphorus, iodine, nickel, tin, iron, selenium, aluminium, and antimony have been analysed by means of the spectrograph, using the discharge-tube method of producing the positive rays. By the analysis of anode rays the constitution of the alkali metals lithium, sodium, potassium, rubidium, and caesium has been determined. The following table gives the collected results and also includes magnesium, calcium, and zinc, whose complex constitution has been determined by Dempster, using his own method of analysis, and beryllium, which has been investigated by G. P. Thomson, using the parabola method.

By far the most important result of these measurements is that, with the exception of hydrogen, the weights of the atoms of all the elements measured, and therefore almost certainly of all elements, are whole numbers to the accuracy of experiment, namely, about one part in a thousand. Of course, the error expressed in fractions of a unit increases with the weight measured,

Table of elements and isotopes.

Element	*Atomic number*	*Atomic weight*	*Minimum number of isotopes*	*Masses of isotopes in order of intensity*
H	1	1.008	1	1.008
He	2	3.99	1	4
Li	3	6.94	2	7, 6
Be	4	9.1	1	9
B	5	10.9	2	11, 10
C	6	12.00	1	12
N	7	14.01	1	14
O	8	16.00	1	16
F	9	19.00	1	19
Ne	10	20.20	2	20, 22
Na	11	23.00	1	23
Mg	12	24.32	3	24, 25, 26
Al	13	26.96	1	27
Si	14	28.3	2	28, 29, (30)
P	15	31.04	1	31
S	16	32.06	1	32
Cl	17	35.46	2	35, 37
A	18	39.88	2	40, 36
K	19	39.10	2	39, 41
Ca	20	40.07	(2)	40, 44
Fe	26	55.84	(1)	56, (54)?
Ni	28	58.68	2	58, 60
Zn	30	65.37	(4)	64, 66, 68, 70
As	33	74.96	1	75
Se	34	79.2	6	80, 78, 76, 82, 77, 74
Br	35	79.92	2	79, 81
Kr	36	82.92	6	84, 86, 82, 83, 80, 78
Rb	37	85.45	2	85, 87
Sn	50	118.7	7 (8)	120, 118, 116, 124, 119, 117, 122, (121)
Sb	51	121.77	2	121, 123
I	53	126.92	1	127
X	54	130.2	7 (9)	129, 132, 131, 134, 136, 128, 130, (126), (124)
Cs	55	132.81	1	133
Hg	80	200.6	(6)	(197–200), 202, 204

Numbers in brackets are provisional only.

but with the lighter elements the divergence from the whole number rule is extremely small.

This enables the most sweeping simplifications to be made in our ideas of mass. The original hypothesis of Prout, put forward in 1815, that all atoms were themselves built of atoms of protyle, a hypothetical element which he tried to identify with hydrogen, is now reestablished, with the modification that the primordial atoms are of two kinds: protons and electrons, the atoms of positive and negative electricity.

The Rutherford-Bohr atom consists essentially of a positively charged central nucleus around which revolve planetary electrons at distances great compared with the dimensions of the nucleus itself.

As has been stated, the chemical properties of an element depend solely on its atomic number, which is the charge on its nucleus expressed in terms of the unit charge, e. A neutral atom of an element of atomic number N has a nucleus consisting of $K + N$ protons and K electrons, and around this nucleus revolve N electrons. The weight of an electron on the scale we are using is 0.0005, so that it may be neglected. The weight of this atom will therefore be $K + N$, so that if no restrictions are placed on the value of K any number of isotopes are possible.

A statistical study of the results given above shows that the natural restrictions can be stated in the form of rules as follows:

In the nucleus of an atom there is never less than one electron to every two protons. There is no known exception to this law. It is the expresssion of the fact that if an element has an atomic number N the atomic weight of its lightest isotope cannot be less than $2N$. Worded as above, the ambiguity in the case of hydrogen is avoided. True atomic weights corresponding exactly to $2N$ are known in the majority of the lighter elements up to ^{36}A. Among the heavier elements the difference between the weight of the lightest isotope and the value $2N$ tends to increase with the atomic weight; in the cases of mercury it amounts to 37 units. The corresponding divergence of the *mean* atomic weights from the value $2N$ has of course been noticed from the beginning of the idea of atomic number.

The number of isotopes of an element and their range of atomic weight appear to have definite limits – Since the atomic number only depends on the *net* positive charge in the nucleus, there is no arithmetical reason why an element should not have any number of isotopes.

So far the largest number appears to be 9 in the case of xenon, which also shows the maximum difference between its lightest and heaviest isotopes,

12 units. The greatest proportional difference calculated on the lighter weight is recorded in the case of lithium, where it amounts to one-sixth. It is about one-tenth in the cases of boron, neon, argon, selenium, krypton, and xenon. No element of odd atomic number has more than two isotopes.

The number of electrons in the nucleus tends to be even – This rule expresses the fact that in the majority of cases even atomic number is associated with even atomic weight, and odd with odd. If we consider the three groups of elements, the halogens, the inert gases and the alkali metals, this tendency is very strongly marked. Of the halogens – odd atomic numbers – all 6 (+ 1 ?) atomic weights are odd. Of the inert gases – even atomic numbers – 13 (+ 2?) are even and 3 odd. Of the alkali metals – odd atomic numbers – 7 are odd and 1 even. In the cases of elements of other groups the preponderance, though not so large, is still very marked. Beryllium and nitrogen are the only elements yet discovered to consist entirely of atoms whose nuclei contain an odd number of electrons.

If we take the natural numbers 1 to 40, we find that those not represented by known atomic weights are 2, 3, 5, 8, 13, (17), (18), 21, (33), 34, (38). It is rather remarkable that these gaps, with the exception of the four in parentheses, are represented by a simple mathematical series of which any term is the sum of the two previous terms. In consequence of the whole-number rule there is now no logical difficulty in regarding protons and electrons as the bricks out of which atoms have been constructed. An atom of atomic weight m is turned into one of atomic weight $m + 1$ by the addition of a proton plus an electron. If both enter the nucleus, the new element will be an isotope of the old one, for the nuclear charge has not been altered. On the other hand, if the proton alone enters the nucleus and the electron remains outside, an element of next higher atomic number will be formed. If both these new configurations are possible, they will represent elements of the same atomic weight but with different chemical properties. Such elements are called «isobases».

It will be observed that the principal atomic species of argon and calcium are isobases, each having a weight 40. In the same manner no less than four seleniums form isobasic pairs with kryptons. In all such pairs known with certainty to exist, the elements concerned have even atomic numbers and even atomic weights, also one member of each pair is an inert gas. The whole-number rule is not to be supposed as mathematically exact, for although the atoms of all elements are made up of the same electrical units their masses will be affected slightly by the way in which these unit charges

are put together. This is called the *packing* effect, and some recent results suggest that the difference caused by it may amount to two or three parts in a thousand in the mass relations of the isotopes of tin and xenon. The packing effect may be clearly expected to be a maximum in the relation between the masses of helium and hydrogen.

The case of the element hydrogen is unique; its atom appears to consist of a single proton as nucleus with one planetary electron. It is the only atom in which the nucleus is not composed of a number of protons and electrons packed exceedingly close together. Theory indicates that when such close packing takes place the effective mass will be reduced, so that when four protons are packed together with two electrons to form the helium nucleus this will have a weight rather less than four times that of the hydrogen nucleus, which is actually the case. It has long been known that the chemical atomic weight of hydrogen was greater than one-quarter of that of helium, but so long as fractional weights were general there was no particular need to explain this fact, nor could any definite conclusions be drawn from it. The results obtained by means of the mass spectrograph remove all doubt on this point, and no matter whether the explanation is to be ascribed to packing or not, we may consider it absolutely certain that if hydrogen is transformed into helium a certain quantity of mass must be annihilated in the process. The cosmical importance of this conclusion is profound and the possibilities it opens for the future very remarkable, greater in fact than any suggested before by science in the whole history of the human race.

We know from Einstein's Theory of Relativity that mass and energy are interchangeable and that in c.g.s. units a mass m at rest may be expressed as a quantity of energy mc^2, where c is the velocity of light. Even in the case of the smallest mass this energy is enormous. The loss of mass when a single helium nucleus is formed from free protons and electrons amounts in energy to that acquired by a charge e falling through a potential of nearly thirty million volts. If instead of considering single atoms we deal with quantities of matter in ordinary experience, the figures for the energy become prodigious.

Take the case of one gram-atom of hydrogen, that is to say the quantity of hydrogen in 9 c.c. of water. If this is entirely transformed into helium the energy liberated will be

$$0.0077 \times 9 \times 10^{20} = 6.93 \times 10^{18} \text{ ergs}$$

Expressed in terms of heat, this is 1.66×10^{11} calories or in terms of work 200,000 kilowatt hours. We have here at last a source of energy sufficient to account for the heat of the sun. In this connection Eddington remarks that if only 10 per cent of the total hydrogen on the sun were transformed into helium, enough energy would be liberated to maintain its present radiation for a thousand million years.

Should the research worker of the future discover some means of releasing this energy in a form which could be employed, the human race will have at its command powers beyond the dreams of scientific fiction; but the remote possibility must always be considered that the energy once liberated will be completely uncontrollable and by its intense violence detonate all neighbouring substances. In this event the whole of the hydrogen on the earth might be transformed at once and the success of the experiment published at large to the universe as a new star.

Biography

Francis William Aston was born in September 1877 at Harborne, Birmingham, England, the third of a family of seven children. He was educated at Harborne Vicarage School and Malvern College where his interest in science was aroused. In 1894 he entered Mason College, Birmingham (later to become the University of Birmingham) where he studied chemistry under Frankland and Tilden, and Physics under Poynting. His winning of the Forster Scholarship in 1898 enabled him to work on the optical properties of tartaric acid derivatives; the results of this work were published in 1901.

Leaving academic life for a time, he worked for three years as a chemist in the laboratory of a brewery. At about this time, however, his interest in physics, rather than chemistry, began to predominate; his aptitude for mechanical contrivance showed itself in his design and construction of new types of pumps for evacuating vessels. From this stemmed his interest in gas discharge phenomena in evacuated tubes.

In 1903 he obtained a scholarship to Birmingham University (as it had now becone) to work on the properties of the Crookes Dark Space in discharge tubes. Within a short time he had discovered the phenomenon which is known as the Aston Dark Space. At the end of 1909 he accepted the invitation of Sir J. J. Thomson to work as his assistant at the Cavendish Laboratory, Cambridge, on studies of positive rays. It was during this period that he obtained definite evidence for the existence of two isotopes of the inert gas neon.

This research was interrupted by the War of 1914–1918, during which time Aston worked at the Royal Aircraft Establishment, Farnborough, where he studied the effect of atmospheric conditions on aeroplane fabrics and dopes (i.e. synthetic coatings).

Returning to the Cavendish Laboratory in 1919, he again attacked the problem of the separation of the isotopes of neon. He quickly achieved success in this by his invention of the mass spectrograph, an apparatus in which the ingenious use of electromagnetic focusing enabled him to utilize the very slight differences in mass of the two isotopes to effect their separation.

Extending this principle to other chemical elements, he discovered, in a series of measurements, no less than 212 of the naturally occurring isotopes. From the results of this work he was able to formulate the so-called Whole Number Rule which states that, the mass of the oxygen isotope being defined, all the other isotopes have masses that are very nearly whole numbers.

Aston continued to make measurements, using an improved instrument, with ever-increasing refinement and precision. He observed and was able to measure those deviations from the Whole Number Rule which were to become so important in the field of atomic energy.

The results of his work were published in the *Proceedings of the Royal Society* and in the *Philosophical Magazine*. He was also the author of the books *Isotopes* (1922; revised edition 1941) and of *Structural Units of the Material Universe* (1923).

Aston was elected to a Fellowship at Trinity College in 1920, in which year he also received the Mackenzie Davidson Medal of the Röntgen Society. In 1921 he was made a Fellow of the Royal Society and was awarded the Society's Hughes Medal the following year, the same year that he received the Nobel Prize. The John Scott and the Paterno medals were given to him in 1923, the Royal medal in 1938, and he was Duddell medalist of the Physical Society in 1941.

He was an honorary member of the Russian Academy of Sciences and of the Accademia dei Lincei, and held honorary doctorates of the Universities of Birmingham and Dublin.

Aston, a bachelor, was an enthusiastic sportsman; skiing, rockclimbing, tennis and swimming were among the sports in which he excelled. He was also a keen musician, playing the piano, violin and the cello.

He died at Cambridge on November 20, 1945.

Chemistry 1923

FRITZ PREGL

«for his invention of the method of micro-analysis of organic substances»

Chemistry 1923

Presentation Speech by Professor O. Hammarsten, Chairman of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

The vast development of chemical science, especially in recent times, is based not only on new concepts and important discoveries, but also on improved experimental equipment and on newly invented and perfected methods. It is also evident that a fundamental improvement of a previously known method can, in certain cases, be of as great a value for further research and for the development of science as a new scientific discovery.

This concept of the significance of an improvement was also expressed by Alfred Nobel, in his great insight, when he stipulated in his will that the Nobel Prize for Chemistry should be awarded to the person « making the most important chemical discovery or improvement » that would most benefit mankind.

The work, which this year has been rewarded with the Nobel Prize for Chemistry by the Royal Academy of Sciences, who awards it to Professor Fritz Pregl of Graz for his invention of the micro-analysis of organic substances, is not a new discovery either. It is in the main a revision and an improvement of older methods.

Nobel's expression – the most important chemical improvement – means that the improvement must be concerned with a particularly important field of chemistry. It is quite evident that this applies to Pregl's work. This work is devoted to the determination of the contents of the different elements in organic compounds, the aim of which is to determine the quantities of the various elements in organic, so-called carbon compounds – whether these compounds occur ready-formed in the animal and vegetable kingdom or have been prepared in a chemist's laboratory. If one wishes to sum up the significance of the field to which Pregl's work belongs, one could say that without this organic elemental analysis there would be no organic chemistry in the scientific sense, neither would we possess the extensive chemical industry that has arisen out of it.

In what does the improvement made by Pregl consist, and what is its significance?

The improvement consists of the fact that Pregl converted previously used methods for quantitative analysis of relatively large quantities of substances to micro-analytical methods. This has made it possible to carry out these analyses of such small quantities of substances, the analysis of which would previously have been impossible, with exactly the same accuracy, but with great savings in time, labour, and expense.

Pregl succeeded, by introducing new apparatus and techniques, in reducing to the almost incredibly small amount of 5–3 milligrams and even less the quantity normally required for the quantitative determination of various elements in organic compounds. The same amount of substances which up to now would have been required for a single carbon-hydrogen determination, is now with Pregl's methods sufficient for up to 50 different analyses. In this way this quantity suffices for several determinations not only of carbon and hydrogen, but also of other elements forming the compound; it also makes possible certain other investigations important for the study of the chemical structure of the compound, its constitution.

When in 1910 Pregl started the investigations which he continued with great skill and success during the following years, he first set himself the task of revising the method for carbon-hydrogen determination, the focal problem of elemental analysis. This part of the work was the most comprehensive and also the one that produced the most difficulties. In close connection with this task he also developed two methods for the micro-determination of nitrogen. Micro-methods for chlorine, bromine, iodine, sulphur, phosphorus, and a great number of metals in organic compounds were developed by him or under his guidance. However, this does not exhaust the range of his many micro-determinations. It is not sufficient to be able to determine with certainty the elemental composition of a substance. The molecular weight must also be known, and for the determination of this he constructed a micro-apparatus which makes it possible to work with such a small quantity as 7–10 milligrams.

To ascertain the chemical constitution of a substance it may also be necessary to determine the quantity of important groups of atoms included in this substance, and apparatus was designed and methods worked out to deal with such cases.

This, naturally, is not the place to give a detailed account of Pregl's methods. Only an expert can really appreciate and correctly assess the value of the various experimental techniques evolved; the difficulties which he had to overcome; the perspicacity and perseverance which were required

in order to achieve a fully satisfactory result by discovering and eliminating countless sources of error. However, already the facts stated here will show the essential significance of Pregl's work.

A method which makes elemental analysis of such small quantities of substances possible must, in many cases, be an inestimable aid for the chemist. If the material to be investigated is hard to obtain, the chemist may be in a very difficult position: the quantity of the product or the products that he has obtained after hard and protracted work is so insignificant that it would have been impossible by the previously known methods even to define the elemental composition, let alone the chemical constitution. This, for instance, arises quite often in work in physiological or pathological chemistry, where the original material is often only obtainable in quite limited quantities, and where new material cannot be procured at all, or only with great difficulty. Many research workers in this field have confirmed the great value of the Pregl method in coming to the rescue and have found it indispensable for the execution of certain investigations.

Pregl's micro-analysis can be equally well applied in all fields of organic chemistry. It has already proved itself in a great number of cases, and has stood the test in this country as well. It opens promising prospects for research in the future, particularly in the vast field of biochemistry. There is every reason to hope that micro-analysis will make possible fruitful study of a great number of substances which so far, in some respects at least, have been practically inaccessible to exact chemical investigation. Such substances, for instance, include enzymes, vitamins and hormones, the extremely great significance of which for the vital processes is well known.

Our knowledge of these substances at present is in the main limited to their effects or the results of their action and the external conditions for these. Only when we have succeeded in unravelling their chemical character will it be possible to gain a deeper insight into their mysterious function, which is at present concealed from us. A thorough chemical investigation of these substances is therefore one of the most important tasks of biochemistry, and, as far as can now be judged, Pregl's micro-analysis offers an extremely valuable, if not indispensable aid for the solution of such a problem.

As usual, the representative of the Academy of Sciences said some personal words to the laureate, congratulated him and asked him to receive the prize from the hands of His Majesty, but unfortunately these words have not been preserved.

Fritz Pregl

Quantitative micro-analysis of organic substances

Nobel Lecture, December 11, 1923

In accepting the honour of addressing this illustrious assembly on this proud occasion today, I am complying with § 9 of the Statutes of the Nobel Foundation, and I would like to take the opportunity at the same time of expressing my humble thanks to the Swedish Academy of Sciences for awarding me the Nobel Prize for Chemistry for the year 1923.

Already two years ago I had the honour of delivering two lectures to experts in the Kemiska Sällskapet (Chemical Society) on the subject of the quantitative organic micro-analysis developed by me. The nature of my task today does not permit me to present all the details described and demonstrated at that time, neither does the time allocated allow me to execute two important experiments; I can therefore only give a survey of the origin, the development and the final results up to date of quantitative organic micro-analysis.

I had felt an inner compulsion to carry out the analysis of organic substances with much smaller quantities than had hitherto been used at a time when I was working on an investigation of a substance which could be obtained in extraordinarily small quantities; I was therefore forced to decide whether to process tons of material or whether to search for new methods, which would enable me to arrive at correct analytical results while using much smaller quantities then previously. I decided on the latter course of action. The most obvious plan was to apply reductions to all and everything, namely to move the decimal point back one or two places, not only in relation to the quantity of the substance, but also in relation to all the apparatus, reagent quantities, etc., involved.

This resulted not only in the necessity of carrying out all weighings with far greater accuracy than the customary analytical balances permitted, but the balance also had to be constructed in such a manner that the diversely shaped devices that were to be weighed could be accommodated on them. The assay balance for precious metals by Wilhelm Kuhlmann in Hamburg, which at that time was already being used in other laboratories for weighing with accuracy of 0.01–0.02 mg, fulfilled these requirements to a high degree.

The designer, most fortunately, carried out great improvements to it at my suggestion, so that it is now possible to weigh with an accuracy of ± 0.001 mg over a range of 20 grams using the micro-chemical balance designed by him and now in common use.

The assumption that our aim could be achieved by shifting the decimal point for all factors proved to be entirely misleading; for, following the reduction of the quantity of the substance, effects appeared which decisively influenced the result of the micro-analysis, whereas they had been insignificant in macro-analysis and had therefore often not even been noticed.

This can already be very simply illustrated in relation to nitrogen determination according to Dumas. The volumetric determination of the nitrogen set free during this process is influenced to such an extent by the 50% potassium hydroxide solution adhering to the interior of the measuring tube of the micro-nitrometer, that 2% must be deducted from the volume reading. Requirements regarding the carbon dioxide used for deaeration and for expelling the nitrogen are very much more exacting than one had hitherto been accustomed, and it was found necessary to develop a carbon dioxide supply which was completely free from air. Up to now there has been no lack of work in this direction and it is peculiar that nearly always the massive, compact marble was suspect as carrier of air; it was even found necessary to boil it off in a vacuum, and the fact was overlooked that aqueous solutions like hydrochloric acid are capable of absorbing considerable quantities of air, and also of nitrogen. Further, it was found to be imperative that the alkali sealing off the volume of nitrogen that had been set free, should not foam; treatment with barium hydroxide was found to be the means by which the substances that caused the foaming could be extracted from the alkaline solution. Finally, the position of the reduced copper mass in the tube lining was found to be of importance and the most correct position proved to be in the middle of the copper oxide lining in the hottest part of the tube.

The development of the determination of carbon and hydrogen was considerably more difficult, because the problem here was firstly to absorb the resulting combustion products free from foreign admixtures and, secondly, in such a manner that the increase in weight could only be related to the resulting water and the carbon dioxide which had been produced. Thus, for instance, even the use of clean air and pure oxygen can result in incorrect weight increase, if the gases are conducted through new rubber tubes, because these release noticeable amounts of vapours containing carbon and

hydrogen into the stream of gas. Artificial ageing, for instance by passing steam through these tubes for one hour, can eliminate this undesirable property.

If the substance which is to be analysed contains nitrogen, halogen, or sulphur, gaseous products may result during combustion, which might erroneously be weighed and recorded as carbon dioxide, because they are also retained by the absorbing agent for carbon dioxide, i.e. soda lime. In such cases, therefore, entry of such products into the absorption apparatus must be prevented at all costs. Whereas for macro-analysis different tube linings are recommended for the various substances in accordance with their composition, my main aim was to develop a tube lining which would always retain everything that was not carbon dioxide or water. I therefore call it the universal lining. It consists of a mixture of copper oxide and lead chromate between two layers of silver and finally a layer of lead peroxide on asbestos heated to 180°C.

Since the invention of Liebig's potassium apparatus and the calcium chloride tube, many variations have been made in the course of nearly a century to the usual absorption apparatus for elemental analysis. I chose for this purpose the simplest form, a tube. It is quite obvious that the slightest impurities must cause special errors. Warming caused by wiping, wrongly makes these small devices appear to be lighter in weight; then, when they have not been filled, they attain a constant weight within 10–15 minutes. However, if they contain an absorbing agent and if their connections are open at both ends and are not tapered, they will increase in weight at the same rate after that period has elapsed, that is to say, they absorb from the air water vapour and therefore become heavier. I have finally succeeded in completely preventing this diffusing-in of water vapour by fitting capillary tapering pieces between larger and smaller expansions of the flow line; this arrangement represents such a gradual diffusion gradient that even for the sensitive weighing instrument of the micro-analyst unnoticeable weight increases during the periods under practical consideration will result.

On the other hand, these capillary taperings present considerable resistance to the gas stream resulting in an increase of pressure in the interior of the combustion tube. New difficulties arose hereby; the tube connections between the apparatuses, particularly between the warm outlet of the combustion tube and the calcium chloride tube – the most critical spot – could cause the loss of combustion products in consequence of the increased pressure, if the tube connection is only slightly damaged, and especially in view

of the fact that rubber has the peculiarity of allowing carbon dioxide to diffuse easily. I eliminated these hazards by equalizing the pressure at the critical place to that outside, i.e. the atmospheric pressure. This effect can easily be achieved by means of a Mariotte's flask.

Right from the start I had rejected the idea of forming the connections between the apparatuses and the combustion tube by ground glass joints and of using cocks for closing the absorption apparatus, because these cannot safely and easily be wiped and would also be in danger of being broken on account of their fragility. On the contrary, I am convinced that micro-analysis, its development and wider use will be best served by avoiding cocks and ground joints.

When all these conditions are observed, it is quite easy to obtain accurate analysis results for 2–4 mg of the substance. The smallest quantity ever used was 1 mg and the divergence was still within the usual permissible margin of error. In doing this we have quite exceptionally reduced the amount of substance required for the analysis. Bearing in mind that Liebig used 0.5 g of substance and originally even 1 g, and that towards the end of the last century 0.15–0.2 g was usually considered to be the quantity required, we may well say that the development of micro-analysis has reduced the quantities required for the determination to about one hundredth part of what ten years ago was considered to be the amount required. This reduction does not impair the accuracy in any way and I can even say that my students demand far greater accuracy from micro-analysis than they previously expected from macro-analysis. This probably follows from the fact that the basic conditions are far better and can be more completely allowed for than was possible with macro-analysis. There are two further advantages that should be borne in mind. Firstly, there are great savings in gas and reagents, and secondly, and this is even more valuable, there is a saving in time. Thus it is possible to attain the same result in at least one third of the time required for macro-analysis; a decision then to repeat micro-analyses is much easier made, as the work is much shorter and more pleasant.

For the determination of halogens and sulphur Carius' method was originally generally used. The precipitates obtained then used to be sucked out in a small Gooch crucible. I particularly would like to mention here briefly that I was the first to recognize that the presence of barium chloride was essential for the decomposition of sulphur-containing substances with nitric acid; without this, losses were certain to result. Later a completely new analytical process for the decomposition of organic substances was discovered, which

consisted in burning them in an oxygen stream and then leading the combustion products over red-hot platinum in order to complete the decomposition. With halogen determinations, these combustion products are collected in an alkaline sulphite solution, whereas the products from sulphur determinations are collected in perhydrol, with which porcelain beads are wetted. All this is done in one single hard-glass tube and this may be used many hundreds of times for the same purpose. All the halogen is obtained with the washing liquid in the form of sodium halide, all the sulphur in the form of sulphuric acid. Here also there were initial difficulties with the determination of the halogen, because the values obtained after acidifying the alkaline sulphite solution with nitric acid were too high. The explanation was that the oxidation of sulphite to sulphuric acid does not proceed directly, but by the precipitation of elementary sulphur, which would indicate that this reaction does not proceed monomolecularly, but probably by way of a polythionic acid. For, if we first use perhydrol as oxidizing agent in alkaline solution and then acidify with nitric acid, sulphur is not precipitated and fully correct results are obtained. The resulting silver halides are automatically sucked on to a filter tube and weighed after drying. Similar analytical instructions resulted with sulphur determinations; if these instructions are observed, correctness of the analytical results can be guaranteed.

My assistant, lecturer Dr. Hans Lieb has developed methods for the determination of phosphorus and arsenic in organic substances, by which satisfactory results are achieved.

Apart from the quantitative determination of the elements making up the structure of organic substances, the quantitative content of certain groups of atoms is also of the utmost importance. I have therefore developed the determination of the carboxyl group by acidimetry by using phenolphthalein as indicator; I have further elaborated the determination of the methoxy and methylimide groups. I do not want to go into details, but would nevertheless stress the enormous simplification of the micro-apparatus as compared with the macro-procedure in connection with the methoxy determination; the weighing of the substance in tin-foil caps is new in principle and of great advantage, as the hydriodic acid does not bump because of its tin iodide content. For the methylimide determination, the fact that the ratio of the hydriodic acid to the substance quantity used (approx. 3 mg) would be far more favourable than for the macro-analytical process, had not been foreseen. This was for the first time noticeable in connection with physostigmine, as only by micro-analytical methods a third methyl or ethyl group was de-

tected, where previously only two had always been assumed, so that the structure of this body had to be revised for this reason.

Determination of the molecular weight by the boiling-point method has also become practicable through micro-analysis, as we are able to obtain reliable values for a quantity of 7 mg.

It is hard to believe that the simplest of all determinations, i.e. the determination of the residue through fuming with sulphuric acid, as is necessary with the determination of Na, K, Ca, etc. in organic substances, could only be adapted in such a way as not to make too great demands on the skill of the analyst and yet give satisfactory results that beginners always think they are mere accidents, long after the previously described difficult methods had been developed.

Finally it might not be superfluous to raise the question what positive results micro-analysis has achieved so far.

In this connection we may mention that one of the first results was the discovery that the yellow colouring matter in corpora lutea of cattle ovaries was by micro-analytical carbon hydrogen determination found to be carotin, the substance which is in carrots widely found in the vegetable kingdom. This was extracted from approximately 10,000 ovaries in the Willstätter Laboratory in Zurich and would have been sufficient for only one macro-analysis. Thus, in this case already micro-analysis has made possible important progress in our knowledge, by proving that the same substance appears as colouring matter in both natural kingdoms, the vegetable as well as the animal kingdom.

Also, in view of the minute quantity of material available, I want to draw your attention to the valuable information on molecular structure obtained by means of micro-analysis, through the work of Adolf Windaus on cymarin and cholesterol, and Wieland's work on the decomposition of bile acids, where micro-analysis proved its value.

Last but not least I want to mention that quite recently a Swede, C. A. Yllner applied micro-analytical methods successfully at my Institute in Graz for the identification of alkaloids in forensic cases, that is, when these had to be extracted from dissected corpses. During the last few years my methods have also been applied in technology for electrolytic metal analysis; and for the analysis of wine very clever micro-analytical methods have been developed, apart from those discussed here.

I therefore am very hopeful that in the future quantitative organic micro-analysis will find many more fields of application and expansion, and that

it will make possible much insight and discernment which otherwise might not have been possible, especially following the magnificent recognition that has been awarded to it by the Swedish Academy of Sciences.

Biography

Fritz Pregl was born in Laibach on September 3, 1869, and attended the local «Gymnasium» (grammar school), from where he proceeded to the University of Graz to study medicine. He received his M.D. in 1894, but even prior to graduation he became assistant lecturer for physiology and histology under Alexander Rollett, taking over the chair when Rollett died in 1903. During this time Pregl also acquired a thorough knowledge of all branches of chemistry under the guidance of Professor Skraup.

In 1904 he went to Germany, where he studied for short periods under Gustav v. Hüfner in Tübingen, W. Ostwald in Leipzig and Emil Fischer in Berlin. On his return to Graz in 1905 Pregl worked at the Medico-Chemical Institute under K. B. Hofmann and was appointed forensic chemist for the Graz circuit in 1907. At that time he started investigating the components of albuminous bodies and the analysis of bile acids. His work, however, was handicapped by the lack of sufficient starting materials and this fact impelled him to look for methods requiring smaller amounts when making quantitative analyses of elements in compounds.

The years 1910–1913, whilst professor at Innsbruck University, were almost entirely devoted to developing the method of quantitative organic micro-analysis. Pregl continued with this work when he was recalled to Graz University in 1913; he was appointed Dean of the Medical Faculty for the year 1916–1917 and Vice-Chancellor of Graz University for 1920–1921.

Initially Pregl's scientific work had been mainly in the fields of physiology and physiological chemistry; later he turned to the study of the constitution of chemical compounds, in particular the investigation of bile acids. By 1912 he was able, by using his own methods of quantitative micro-analysis, to make measurements of carbon, hydrogen, nitrogen, sulphur, and halogen, using only 5–13 mg of starting materials with results as accurate as those obtained by macro-analysis. Later he perfected his techniques so that as little as 3–5 mg were adequate. Pregl also contributed a number of micro-methods for measuring atomic groups and developed a series of apparatus, including a sensitive microbalance, necessary for his work.

Recognition for his work was first accorded with the Lieben Prize for Chemistry from the Imperial Academy of Science in Vienna (1914), an honorary doctorate in philosophy from the University of Göttingen (1920); in 1921 he was elected Corresponding Member by the Academy of Sciences in Vienna. The greatest and most unexpected honour was the award of the Nobel Prize for Chemistry by the Swedish Academy of Sciences in 1923. O. Hammarsten, the Chairman of the Nobel Committee at the time, pointed out that it was not for a discovery, but for modifying and improving existing methods that Pregl was awarded the prize.

Pregl had, in the early stages of his investigations, avoided publishing individual reports on his experiments, until he had convinced himself that his methods did not only work in his own, but also in other laboratories. He then, in 1917, set down his findings in a monograph entitled *Die quantitative Mikroanalyse* (published by J. Springer, Berlin). A second edition was published in 1923 and a third revised and enlarged edition (256 pages) appeared in 1930. Later editions were revised by Dr. H. Roth. The seventh edition was published in 1958 by Springer in Vienna. Pregl's monograph has also been translated into French and English.

Following the award of the Nobel Prize for Chemistry in 1923, chemists from all over the world came to the Medico-Chemical Institute in Graz to study Pregl's techniques of quantitative organic micro-analysis under his guidance.

Pregl never married, and died after a short illness at the age of 61 at Graz on December 13, 1930. Shortly before his death he put a considerable amount of money at the disposal of the Vienna Academy of Sciences for the promotion of micro-chemical research, stipulating that the interest from this fund was to be used each year to award a prize for outstanding work to Austrian micro-chemists. Since then, the Vienna Academy of Sciences has awarded this prize as the « Fritz Pregl Prize ».

Chemistry 1924

Prize not awarded.

Chemistry 1925

RICHARD ADOLF ZSIGMONDY

«for his demonstration of the heterogeneous nature of colloid solutions and for the methods he used, which have since become fundamental in modern colloid chemistry»

Chemistry 1925

Presentation Speech by Professor H. G. Söderbaum, Secretary of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

Around the middle of the 19th century the English scientist Graham put forward a new principle of subdividing matter by classifying all substances into one of the two great classes: crystalloids and colloids. A crystalloid, e.g. common salt, is characterized in that it passes in the dissolved state readily through membranes such as parchment paper or collodion films and also that it exhibits a rapid free diffusion. A colloid, on the other hand, e.g. glue, is unable to pass through such membranes and diffuses extremely slowly, in contrast to the crystalloid. In passing it may be mentioned that the name colloid originates precisely from κολλα, the Greek word for glue. Other examples of colloids well known to everyone are proteins, starch, rubber, water glass, etc.

It was very soon found that sometimes one and the same substance can occur in one case as a crystalloid and in another case as a colloid. For instance, gold with mercury produce a crystalloidal solution, whilst gold in an aqueous solution exists only in the colloidal state. It is consequently more correct to differentiate between crystalloidal and colloidal *states* rather than between crystalloidal and colloidal *substances*. When it then became a question of forming an opinion of the reason for these different states, several people, e.g. the American scientist Lea, had recourse to the concept of allotropy which existed previously in chemistry, and was illustrated by the typical example of phosphorus with its two so-called allotropic modifications, the yellow and the red. Others again imagined the difference to be that the colloidal solutions were not uniform throughout, not homogeneous as the crystalloidal ones, but that they contained particles, molecule aggregates, of a size which exceeded by many times the size of the molecules in a crystalloidal solution. But which of the two interpretations was the correct one?

This difficult problem was brought a decisive step nearer to its solution by the invention of the *ultramicroscope* at the beginning of the 20th century. The idea originated from Zsigmondy and was developed in detail by him in cooperation with Siedentopf, an able optician with the firm of Zeiss. The

principle of this instrument is briefly that the intensely illuminated object, the solution to be examined, is observed by means of a microscope from the side, i.e. vertically to the axis of the incident light beam. In this way it is possible to differentiate between particles of such small size that they could not be observed under an ordinary microscope, just as the dust particles suspended in the air in our rooms, which are invisible under ordinary conditions, sometimes become visible when the sun's rays shine through the window in a definite direction in relation to the observer. With the ultramicroscope, and especially the improved type which is called the immersion ultramicroscope, progress has been such that particles with a diameter of down to 8 $\mu\mu$ are recognized with arc-light illumination, and down to 4 $\mu\mu$ when using the sun as the light source.

Zsigmondy now found that various gold colloids prepared by him contained delimited particles under the ultramicroscope although they had appeared completely homogeneous under an ordinary microscope. He further showed by a systematic study of the gold colloids that they can be produced in a varying distribution of fineness, onwards from colloids the particles of which are invisible even in the ultramicroscope, up to ones whose particles lie at the limit of visibility in the microscope. He showed that Lea's solutions of so-called allotropic silver are really built up from small, ultramicroscopic silver particles. He finally showed that the examination of other colloids also gave similar results. This proved the correctness of the particle hypothesis, and the heterogeneous nature of colloidal solutions was established. It has also been possible to determine quantitatively the size of the particles. The procedure is to delimit optically a small volume of the colloid to be examined, after which the number of particles in it is counted. If the mass concentration of the colloid is known, it is easy to obtain the mass of the particles, and from this – assuming, for example, a spherical shape and normal specific gravity – the size can be calculated.

As mentioned, there are colloids which are so fine-grained that their particles cannot be distinguished even in the ultramicroscope. However, Zsigmondy has made also these accessible to scientific observation by the invention of the so-called *nucleus method*. This was also first applied to gold, the classical metal of colloid research, and it is carried out by introducing the fine-grained gold colloid into a reducing solution from which metallic gold is slowly precipitated. This now settles on the invisible, colloidal gold particles so that they – the so-called gold nuclei – gradually increase in size, and finally become visible in the ultramicroscope. In this way gold particles with

a diameter of down to $1\frac{1}{2}\ \mu\mu$ have been measured, and it has become possible to determine the particle size – thus, the degree of heterogeneity – in the case of all gold colloids. It was possible to apply the method later to a large number of other metals, and it has proved to be of the greatest importance for a whole number of investigations which had the object of establishing general principles for colloids, indeed it may seem doubtful whether these investigations could have been at all possible without Zsigmondy's nucleus method.

It is a generally known fact that when a colloidal solution, for example one of protein, is treated with certain substances such as salts or acids – in short, electrolytes – it coagulates or «solidifies to a jelly», i.e. it passes into a semi-solid form or a so-called gel. Corresponding, although not completely similar, conditions also arise in regard to colloidal metals, the reason being that the primary particles join together to form large aggregates, i.e. they increase in size whilst diminishing in number.

Zsigmondy's work has quite simply been pioneering as regards the explanation of the mechanism of the coagulation phenomenon and also as regards the study of the structure of gels. It has been found that coagulation progresses extremely slowly at a low concentration of the electrolyte, whilst with increasing concentration the rate of coagulation gradually increases up to a certain stage – at the so-called threshold value – when it rapidly reaches a limiting value which then no longer increases further or changes when the concentration is further increased. Within the rapid coagulation, as Zsigmondy found, the coagulation time is independent not only of the concentration of the electrolyte but also of its nature, whilst on the other hand, the threshold value and the rate within the range of slow coagulation are characteristic for each individual electrolyte.

Based on these facts, Zsigmondy expressed several important fundamental ideas for explaining the coagulation mechanism which were later formulated more accurately and developed to a mathematical theory of coagulation by Smoluchowski. In turn, Zsigmondy and his pupils have been able to verify experimentally this theory in its various details whereby its great general validity has been proved in a brilliant manner.

The brief review given here of some of the most important work of Zsigmondy is necessarily highly incomplete, if not to say fragmentary, but should surely suffice to show how it pioneered the way and opened up new regions in a field of research which had so far been difficult of access, a field which must be recognized as having the very greatest importance for human know-

ledge. Let us only remember in this connection that all manifestations of organic life are finally bound to the colloidal media of the protoplasm.

This by way of motivation for the decision of the Academy of Sciences to award the Chemistry Nobel Prize for 1925 to Dr. Richard Zsigmondy, Professor of Chemistry at the University of Göttingen, for proving the heterogeneous nature of colloidal solutions and for the methods used which have laid the foundation of modern colloid chemistry.

Professor Zsigmondy. When the Royal Swedish Academy of Sciences after mature consideration decided to award you the Nobel Prize in Chemistry for the year 1925, it did this in the firm conviction that it would only be making itself the executor of the unanimous verdict of the entire scientific world.

Convinced that the significance of your pioneering work which is generally recognized today, will in future times stand possibly in an even clearer light, the Academy allows itself to offer you its sincere congratulations on the well-deserved reward the external insignia of which you are now about to receive.

Richard A. Zsigmondy

Properties of colloids

Nobel Lecture, December 11, 1926

Even in prehistoric times the peoples must have become familiar with the properties of colloidal solutions and with their changes. The curdling of milk and the clotting of blood were certainly known to our oldest ancestors.

Colloids have appeared, though sometimes only temporarily, also in chemical operations as carried out by the alchemists, the iatro-chemists and the classical chemists.

Even in the Middle Ages the properties of «aurum potabile» were observed, and of works of the older chemists of the classical period mention may be made of only one investigation by the Swedish scientist Carl Wilhelm Scheele who was at the time the greatest of them all and who described in his work *Om Brunsten eller magnesia nigra* not only the discovery of three elements and their compounds, but also a colloidal solution of manganese dioxide in hydrochloric acid with the following words:

« När Salt-syran stått öfver Brunsten uti kölden, bekom hon en dunkel rödbrun färg (par. 6, a). Emedan Brunstenen, utan at förbinda sig med phlogiston, icke gifver någon färg-lös solution, så följer, att Salt-syran kan lösa honom utan detta principium: Men en sådan solution har antingen en blå eller röd färg (par. 14, No. 4). Färgen är här mera brun än röd; orsaken är, at i denna röda solution de aldra finaste delar af Brunsten simma, hvilka icke så lätt sjunka; ty utom dessa fina partiklar, är denna solution röd, och rödt blandadt med svart, gör brunt. Brunsten har här fästat sig så löst vid Acidum salis, at vatten kan praecipitera honom, och detta praecipitat förhåller sig som ordinair Brunsten. Då nu blandningen af Brunsten och Spiritus salis sattes i digestion, upkom fräsning ock lukt af Aqua regis (par. 6, b).»

For the benefit of the reader who might not understand the Swedish text I give here the translated extract from the German translation of the Proceedings of the Royal Swedish Academy of Sciences from *Neueste Entdeckkungen in der Chemie* (Latest discoveries in chemistry), by D.L. Crell, Vol. 1, page 127, Weygandsche Buchhandl., Leipzig, 1781:

« The hydrochloric acid receives from the manganese dioxide in the cold a dark red-brown colour (par. 6, a). It consequently dissolves it without addition of phlogiston (par. 14, No. 4). The brownness is derived from the very fine particles of manganese dioxide which float about and without which the solution appears red. The manganese dioxide adheres so loosely to the acid that it can be precipitated by water, and this precipitate behaves like ordinary manganese dioxide. When the mixture of manganese dioxide and hydrochloric acid is digested, there appears an effervescence and a smell of aqua regia (par. 6, b). »

Scheele, therefore, has described here an unstable colloidal solution of manganese dioxide in hydrochloric acid which, when diluted with water, allows the manganese dioxide to be precipitated.

This reported case of the occurrence of a colloid does not stand alone. Even in the year 1665 gold purple had been described by Andreas Cassius and his son. This purple proved to be a tested dye for glass melts, naturally without its colloidal nature being recognized.

It is known that the great Swedish scientist Berzelius, the most eminent chemist at the time, made a detailed study of the purple of Cassius. He had, however, paid attention also to other colloids; for instance, he observed the occurrence of the hydrosols of certain sulphides, e.g. arsenic sulphide. He first described the straw-yellow liquid which is obtained by passing hydrogen sulphide into arsenious acid, as a solution of arsenic sulphide owing to its homogeneous appearance; later, however, he added the remark that this liquid should probably be regarded as a suspension of arsenic sulphide because it settled out. Here already the difficulty of classifying such preparations appears. It does not, therefore, seem to be particularly remarkable that a detailed concern with such little defined systems appeared to be unrewarding and was neglected at the time, in view of the wealth of knowledge in the organic field.

Biological and technical problems, however, led again and again back to the question as to the nature of colloids.

For instance, Nägeli carried out more than 50 years ago a masterly investigation into the nature of starch. Also the zoologist Bütschli and the physicist Quincke as well as the chemist Selmi were concerned in detail with phenomena which we know today to be partly characteristic of colloids. The first fundamental explanation we owe to the observations of Graham who gave a masterly interpretation of them and who created a division of solutions into crystalloids and colloids on a broad experimental basis.

He was also responsible for the expressions hydrosol (an aqueous colloidal solution) and hydrogel (the jelly derived from it).

As regards myself, dealing with several technical problems provided the incentive to concern myself with colloids.

I was dealing with gold orpiment glass and with certain ceramic dyes which were based in principle on extremely fine gold divisions. It seemed to me particularly remarkable that the effect of very closely allied chemical compounds could be fundamentally different in regard to the preparation and appearance of these dyes. This observation seemed to me all the stranger as compounds with completely opposite properties frequently produce similar effects on the dyes of extremely finely divided (i.e. colloidal) gold.

These results could not be brought into harmony with the previous experience of chemistry. Consequently, I sought to discover the reason for these phenomena in a way other than the purely chemical one. The first special object of such investigations was the *purple of Cassius*. It is known that Berzelius had regarded it as a chemical compound. The reasons which he gave for this were extremely convincing so that I at first believed that I should not ignore them. On the other hand, however, I also knew that earlier and later workers on the purple of Cassius had regarded it also for weighty reasons as a mixture of finely divided gold and stannic acid. My object now was to decide with full certainty which of these two views was correct. For this purpose an attempt to synthesize the purple of Cassius from very finely divided metallic gold and colloidal stannic acid was to be made. Success or failure of this experiment had to provide the decision in view of the chemical inertness of gold, provided it was possible to prepare it in a sufficiently fine division free from gold compounds and colloidal impurities. Only when I had succeeded in reaching this aim, did I hear of the investigations of Faraday who had prepared extremely fine divisions of gold by the reduction of gold salts. If I had known of Faraday's results, it would have saved me much unnecessary work.

I had taken another path which led me eventually to the preparation of practically equal-sized red gold hydrosols (colloidal gold solutions) by the reduction of gold chloride with formaldehyde in a weakly alkaline solution.

After Faraday's publication was available to me, I followed him and used phosphorus as the reducing agent.

However, as I was able to use the experience which I had gained with the formaldehyde gold, I arrived, when using phosphorus, at extremely fine gold

divisions of almost molecular size, such as were used later by The Svedberg in his diffusion experiments.

But the safest method, at the time, of preparing pure highly red gold hydrosols remained first of all the formaldehyde method. This gave me adequate amounts of sufficiently pure highly red colloidal gold. It was used for trying to synthesize the purple of Cassius, and when this attempt succeeded, it provided proof for the view which regards purple of Cassius as a mixture of finely divided gold with colloidal stannic acid. As on the other hand, the purple behaved exactly like a chemical compound as Berzelius had already pointed out, I arrived at an experience which is important for evaluating colloidal precipitates and which has to be applied right down to the present day for evaluating colloidal systems unless one wants to be a victim of errors, and which can be expressed briefly as follows:

A colloidal mixture may sometimes behave like a chemical compound and has frequently simulated one.

Several of the red gold divisions prepared with formaldehyde as well as those reduced with phosphorus appeared perfectly clear in ordinary daylight (like good red wine). They did not settle out their gold, and I was therefore able to call them rightly *solutions*. In Graham's dialysis, however, they behaved like colloidal solutions. The gold particles did not pass through the parchment membrane. This showed my gold divisions their proper place, namely, that they belonged to the colloidal solutions.

My first publication on gold solutions was followed by quite disagreeable discussions. Other scientists who repeated my experiments without taking the necessary care, obtained strongly turbid and sometimes precipitating liquids, and generalizing their own experiences, called also the gold liquids obtained by me suspensions. This view was supported by the low osmotic energy emission, the absence of a measurable freezing-point reduction, etc. as well as by the fact that even clear gold solutions showed a Faraday-Tyndall light cone and appeared in this sense non-homogeneous.

Had I conceded that my gold solutions were simply to be regarded as suspensions, it would not only have given a completely wrong picture of their character, but if I had classified my gold divisions under such well known systems as suspensions, there would have been no reason for me to concern myself with the following questions which have become extremely important for colloid chemistry:

1. What particle size have colloidal particles? Are they molecules or aggregates of molecules? How many atoms approximately does a single gold particle contain?

2. Why is the emission of osmotic energy so low with gold solutions? Do colloidal solutions perhaps really exert no osmotic pressure, as was frequently believed at the time?

3. Is the Faraday-Tyndall light cone, which by the way is observed in all colloidal solutions, an essential characteristic of them, or is this light cone rather incidental?

Question 1 regarding the particle size was decided in 1902 and later by ultramicroscopy.

The correct answer to Question 2 is given by the masterly work of The Svedberg and Perrin.

Question 3 I hoped to be able to decide already in 1900 by viewing the light cone under the microscope.

Just as liquids of equal gold content can appear differently under ordinary viewing, so the intensity of the Faraday-Tyndall light cone can vary in solutions which appear externally clear when viewed with the naked eye.

In apparently similar solutions of clear appearance the light cone sometimes occurs very intensely, and almost disappears in other cases, e.g. in several gold solutions reduced with phosphorus.

In a preliminary experiment it was found that the light cone could easily prove the presence of one-hundredth part of the substance which Bunsen and Kirchhoff had proved by spectrum analysis.

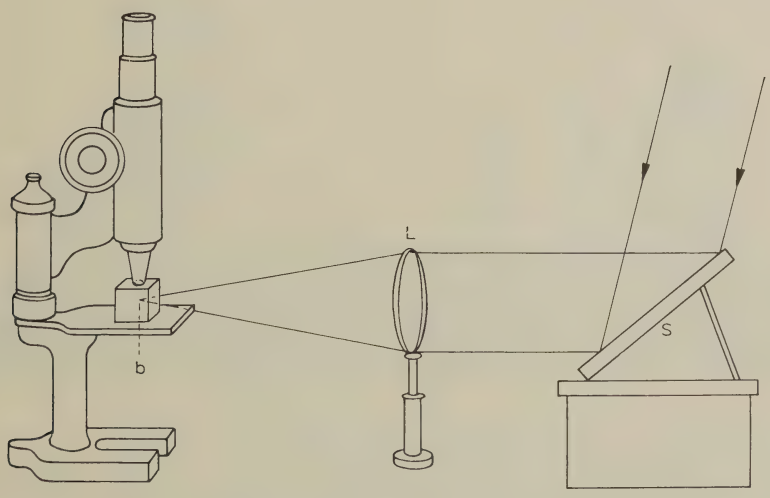


Fig. 1. The first arrangement for making ultramicroscopic particles visible.

Viewing of the light cone under the microscope (Fig. 1) gave the following:

(1) In strongly turbid liquids thousands of individual particles of different colour were recognizable.

(2) Clear gold solutions with a medium strong Tyndall cone, however, showed under the microscope a light cone which disappeared when the solutions were diluted without being able to make individual particles visible.

(3) Very fine gold divisions obtained with phosphorus showed several gold-coated dust particles, but the liquid between them appeared optically empty.

The addition of common salt showed, however, that the clear liquid contained elementary gold. The salt coagulated the colloidal gold solution, the gold was precipitated in the form of coarser aggregates, and thousands of yellow-brown gold particles filled the liquid.

Much was explained by this, but for some questions simple viewing of the light cone under the microscope was not sufficient. My endeavour was to develop the microscopic viewing of the light cone to its highest perfection.

Jointly with H. Siedentopf in Jena, therefore, the method was developed further. An instrument of high capacity was made with which gold particles

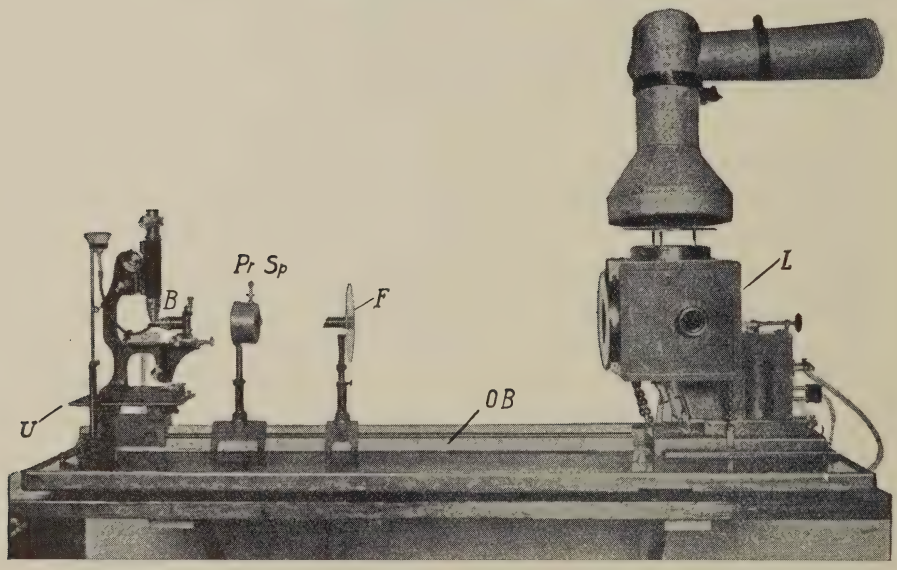


Fig. 2. Immersion ultramicroscope.

L = Light source; F = Telescope objective which gives a picture of the light source on the precision slit $PrSp$. The condenser B forms an image of the precision slit in the colloidal solution, which is in a small dish.

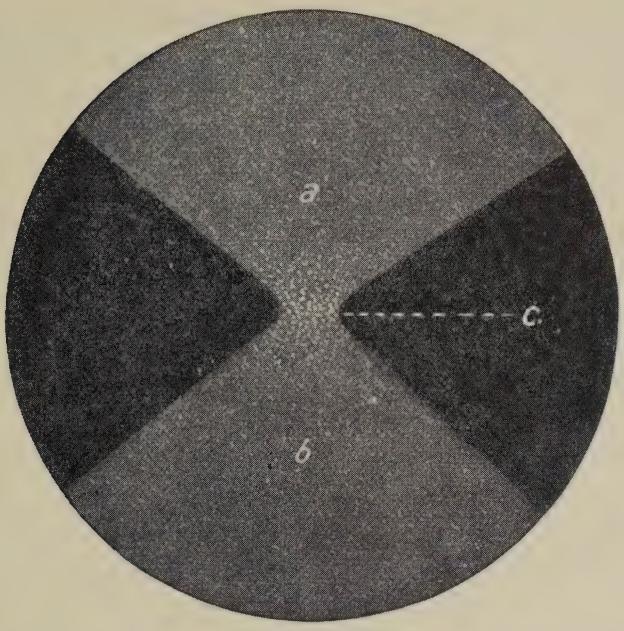


Fig. 3. Ultramicroscopic picture when using the bilateral slit *PrSp*. The picture of the slit is at *C*, the narrowest constriction.

with a diameter of down to 10 mμ could still be made visible in sunlight: the slit-ultramicroscope.

With this instrument it was then possible to carry out size determinations of the gold particles by counting the particles in a certain volume of colloidal gold solution the gold content of which was known.

Similarly the number of gold particles in gold orpiment glass was determined.

A preliminary check of the accuracy of the size determination was obtained by comparing the brightness of the ultramicroscopic pictures.

In passing the following may be mentioned: The knowledge that very small particles can be made visible by very bright illumination on a dark background (i.e. in a dark field) led to substantial improvements of the so-called dark-field condensers which in connection with microscopes were later often called ultramicroscopes.

Several inventors were concerned with the improvement of such condensers: Siedentopf built the paraboloid and the cardioid condenser; Reichert the mirror condenser; Ignatowski and Jentzsch other condensers, for instance, the concentric ball condenser. I myself improved the method of intense illu-

mination from one side by designing the immersion ultramicroscope which is manufactured by the optical workshops of the firm of R. Winkel in Göttingen (cf. Figs. 2 and 3).

Observations by H. Ambronn on dichroism, and work carried out by me in Jena jointly with H. Ambronn, and also the behaviour of orpiment glass made it appear probable even in 1904 that the small submicroscopic gold particles were crystalline.

The application of Tammann's theory of crystallization to the formation of the gold hydrosols appeared, therefore, promising. It led not only to an explanation of hitherto unexplained phenomena in the preparation of orpiment glass, but also to the discovery of the nucleus method. This gives gold solutions of definite particle size.

Later much use was made of the nucleus method, both in the preparation of gold solutions for physical investigations and for determining the pore size of fine filters.

I mention in particular the well-known investigations of The Svedberg and Arne Westgren.

Electrical Charge and Coagulation – The gold particles of colloidal solutions have a negative electrical charge, just as those of many other irreversible colloids. The electrical charge is very important with these colloids as it is the main cause of their stability. If this charge is taken away from the particles, say by adding salts, particle aggregation immediately occurs and the system coagulates. Externally this is noticeable with colloidal gold by the change in colour from red to blue. In the ultramicroscope not only a colour change

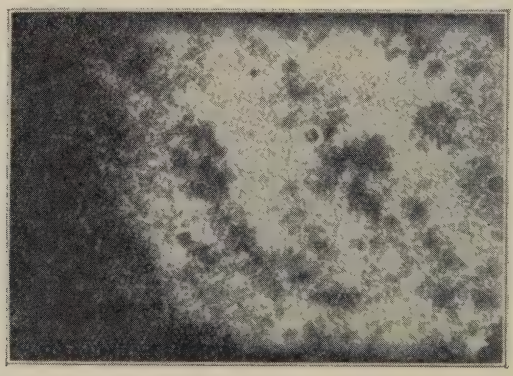


Fig. 4. Gelatine gel photographed by Bachmann. The black areas are optically empty liquid in which single submicrons are moving. The bright areas are jelly flakelets which diffract light.

of the individual particles is noticed, but also an important change in the number of the particles.

The coagulation can be interrupted at any moment by the addition of protective colloids. It is, therefore, possible to determine the number of ultramicrons present after each definite period of time after adding the coagulating agent, and consequently the speed of the coagulation. With ordinary gold hydrosols the particle aggregation occurs extremely rapidly. Dilution with water, however, retards the aggregation of the particles owing to the increase in the mean distance between the particles. In spite of the dilution coagulation generally takes place very rapidly, provided that a sufficient amount of precipitating salts is added, so that it originally appeared as if the submicroscopic particles attracted one another over rather large distances.

This induced me to ask the theoretical physicist M. von Smoluchowski to derive an experimentally verifiable formula by which the presence of spheres of attraction could be deduced from the speed of coagulation; von Smoluchowski willingly agreed to my suggestion and gave, in addition, a complete theory of coagulation on a mathematical basis.

My own experiments as well as those of Westgren and Reitstötter led to the surprising result that the spheres of attraction of the gold particles slightly exceed twice the particle radius, in other words, that these particles must almost be touching one another before they unite irreversibly.

Further investigations in this field have been made with other systems, among others by Richard Lorenz, by Kruyt (Utrecht) and G. Wiegner (Zurich) with their pupils.

With these expositions we approach an interesting field which is called changes of state of colloidal solutions. The majority of these changes is due to unification or separation of the particles. The former of these processes can proceed in different ways; only two of them may be emphasized here – the unification of particles by aggregation and by crystallization.

Gel Structures – The changes of state are particularly striking in the formation of a jelly. They are accessible to direct observation in the ultramicroscope, and W. Bachmann has made in the Institute placed under my direction a detailed examination of various jellies both during and after their formation. He worked with various dark-field condensers, for instance with Siedentopf's cardioid condenser (Figs. 4, 5 and 6).

The most important result of these investigations can be summarized in that in general jelly structures can be of very different nature. They appear

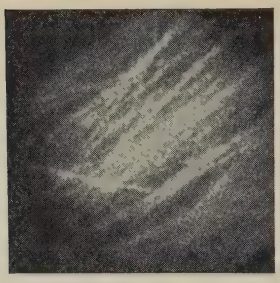


Fig. 5. Picture of 20 % sodium oleate jelly; solidified slowly (at approx. 10°). Apochromat 3, ocular 1, magnification 140. Cardioid condenser (Siedentopf).

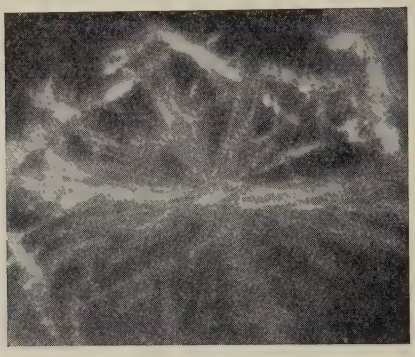


Fig. 6. Picture of 5 % sodium palmitate jelly. Concentric condenser (Jentzsch).

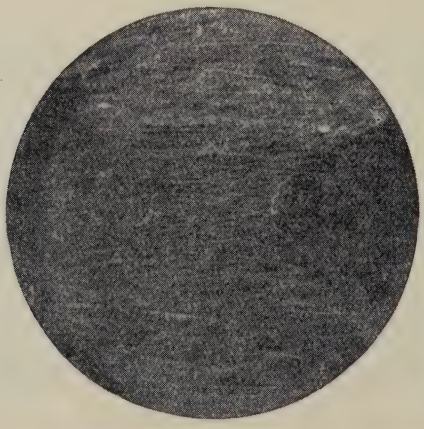


Fig. 7. Filament structure in the vitreous body of the eye from a drawing by Dr. Heesch. (From *Kolloidchem. Beih. Ambronn-Festschr.*, 1926).

sometimes as predominantly grainy structures (as in the case of gelatine) or also as networks of very fine filaments or long-drawn crystals as, for example, in gels of soaps.

Of particular interest in this connection is the ultramicroscopic structure in the vitreous body of the eye which was discovered by Thiessen and Baurmann with the aid of the immersion ultramicroscope. It consists of a maze of fine filaments of proteins, filaments which are submicroscopic in two dimensions but microscopic in one. This maze of filaments imparts to the vitreous body its elasticity, and the change of the filaments which occurs with time and is visible in the ultramicroscope produces a melting away of the jelly. More recent investigations of the vitreous body have been made by C. Heesch, Göttingen. (Fig. 7).

The gel structures are frequently so fine that their observation is no longer accessible to ultramicroscopy. Such systems occur, e.g. in the dry gel of silicic acid.

This appears to be homogeneously transparent, but is permeated with an immense number of amicroscopic voids which may be filled with all kinds of liquids.

Van Bemmelen was the first to determine in careful investigations the reduction in vapour pressure which the water in such systems undergoes.

Further investigations in my Institute (in particular an excellent work by J. S. Anderson) led to the valuable result that the vapour-pressure reduction in the gel of silicic acid is essentially due to the development of concave menisci in the ultramicroscopic pores of the gel when the liquid dries out.

By using a formula from capillarity theory it now became possible to determine the diameter of the voids in a given gel from several series of experiments independently of one another with good agreement. This diameter is variable, very small and can be measured in millionths of a millimetre.

Since then the gel of silicic acid is also used technically for the condensation of liquid vapours, similarly to absorption charcoal.

Transport of Electricity by Colloidal Particles – More than twenty years ago the statement was sometimes made that the conductivity of colloidal solutions was due only to impurities from crystalloid-dissolved electrolytes. This seemed to me *a priori* improbable because electrically charged colloidal particles which move in an electric current, would have to participate in the transport of electricity in the same way as ordinary ions; there only remained the question what share the colloidal particles have in the transport of electricity. It

was, therefore, first of all necessary to separate the colloidal solutions from the admixed electrolytes. This was done by ultrafiltration, a method which had already been used by Duclaux. The further pursuit of this object by my pupil G. Varga (he examined colloidal stannic acid) then led not only to an answer to this question, but also to a preliminary evaluation of the composition of the particles in the hydrosol of stannic acid.

Other investigations by R. Wintgen and his pupils then confirmed Varga's findings and gave, in addition, information on the electrical equivalent and the composition of the particles in the colloidal solutions of iron oxide and chromium oxide so that we are now completely informed about the actual character of certain colloidal particles. Over and above this, the method used in these investigations promises, when applied to other colloids, to give further information on the composition and nature and magnitude of the charge of micelles. This expression which was first clearly defined by J. Duclaux denotes the colloidal particle with the charging ions adhering to its surface and the ions dissociated from it which compensate the charge of the particle externally. The concept « micelle » has proved to be extremely fruitful in evaluating the composition and the electrical behaviour of colloidal particles.

Structure of the Particles – An important question concerns the form and shape of colloidal particles and the nature of their space filling. The ultramicrons are in many cases not iso-dimensional, i.e. not spheres, cubes, or octahedrons, as is usually assumed as a first approximation for the purposes of mathematical treatment. Frequently they are extended in length (filaments, lamellae or platelets), analogous to the description in the discussion of gel structures.

Sometimes it is possible to observe rodlets directly in the ultramicroscope. In hydrosols of vanadium pentoxide and benzopurpurin such formations have frequently been observed.

Experiments on the peptization of stannic acid and purple of Cassius had early shown that the peptization, i.e. the transition from hydrogel to hydrosol under the influence of electrolytes, is always connected with an electrical charging of the particles to which the mentioned change of state is due.

The electrically charged particles are distributed evenly in the surrounding liquid, thus forming a hydrosol. Depending on the amount of peptizing electrolyte finer or coarser divisions are obtained, as can be proved by ultramicroscopy and ultrafiltration (Dissertation by Heinz).

The study of these systems has led to the result that the particles of such hydrosols or colloidal solutions obtained by peptization are as a rule not to

be regarded as being solidly filled. In other words: these solutions contain secondary particles which can be imagined as being composed of many smaller, solidly filled primary particles. The words primary and secondary particles were first used by Werner Mecklenburg.

The picture which we obtain when we consider also the colloidal solutions in addition to the gases and the crystalloidal solutions, is roughly as follows:

In the gaseous state and in crystalloidal solution the substances are always subdivided down to their molecules, they move freely and independently of one another, and they obey the gas laws.

The fact that the molecular weight of chemical compounds could be calculated from the vapour pressure and osmotic measurements, is due to the fact that the molecules of a given chemical compound are all equal to one another.

The peculiarities of electrolyte solutions found their explanation in the dissociation theory of Svante Arrhenius.

The particles of colloidal solutions are larger than the molecules, and must frequently be regarded as aggregates of molecules; they may be of different size even when we are dealing with solutions of the same substance. However, the same laws apply to them which the molecular theory set up for molecules. Owing to the difference in their mass, however, it is not possible to determine exactly the molecular weight of the dissolved substance from osmotic measurements, but on the other hand, the particles often have the advantage of being directly visible. In this way we gain an insight into their absolute size in another way.

The foregoing remarks were able to deal, if they were to fit the occasion, only very briefly with the state of the knowledge of colloids which has been reached in connection with my own investigations. We possess today extensive knowledge of the size and structure of colloidal particles and proved methods for their investigation. I was able to express myself here all the more briefly as I have given a detailed description with literature references in my *Lehrbuch der Kolloidchemie* (5th ed., Leipzig, 1925 and 1927).

Although we should not be satisfied with what has been achieved, the hope does not seem to us too bold that we shall be able to build safely on the basis that has been won the further knowledge of colloids as a continuation of the proved molecular theory and its impressive extension through the ionic theory of Svante Arrhenius.

Biography

Richard Adolf Zsigmondy was born in Vienna on April 1, 1865. His father, doctor Adolf Zsigmondy, had done a great deal to promote dentistry in Austria, had invented several surgical instruments and devices, and had published several scientific and medical works. He encouraged his four children's interest in the natural sciences. He died when Zsigmondy was only 15 years old. Zsigmondy's mother, Irma von Szakmáry, encouraged her children to lead an outdoor life, to take an interest in the arts and to follow their own inclinations. Zsigmondy and his brothers spent much of their time climbing, mountaineering, swimming and diving.

Zsigmondy's interest in chemistry and physics developed at an early age; he studied Stoeckhardt's textbook *Schule der Chemie* and carried out many of the experiments mentioned there in his own small laboratory in his home. He was also influenced by Roscoe-Schorlemmer's und Berzelius's textbooks on chemistry.

Under the guidance of Professor E. Ludwig of the Medical Faculty in Vienna he learnt the basic facts about quantitative analysis. He then studied at the Technische Hochschule in Vienna and in 1887 went to Munich to read organic chemistry under Professor W. von Miller. After taking his doctorate, he remained as Professor von Miller's assistant and later accepted a similar position as assistant to the physicist Professor Kundt in Berlin. In 1893 he qualified as lecturer at the Technische Hochschule in Graz and also accepted a teaching post there. His work on lustre colours for glass and china induced him to study more closely the chemistry of colloids, and led to an appointment with the glass works Schott und Genossen in Jena, where he remained until 1900. He left in order to exclusively pursue scientific research. During this period he discovered how to prepare reproducibly gold hydrosols and also developed the slit-ultramicroscope in joint collaboration with Siedentopf.

In 1907 Zsigmondy was appointed Professor and Director of the Institute of Inorganic Chemistry at the University of Göttingen, where he remained until his retirement in February 1929. Following the First World War, es-

pecially in 1922 and 1923, the Institute suffered severe shortages of the most simple chemical materials and scientific research work became very difficult. In 1925 Zsigmondy was awarded the Nobel Prize for Chemistry for his work on the heterogeneous nature of colloidal solutions. This made it possible for him to overcome, with deep gratitude, most of the difficulties he had encountered in the previous years. Apart from his *Lehrbuch der Kolloidchemie*, Zsigmondy published a book *Über das kolloide Gold* in collaboration with P. A. Thiessen. His son-in-law, Dr. Erich Hückel, who was also one of his co-workers, contributed a book on the theories of adsorption for Zsigmondy's collected papers *Kolloidforschung in Einzeldarstellungen*.

Zsigmondy married Laura Luise, *née* Müller, the daughter of Professor Wilhelm Müller, lecturer in pathological anatomy in Jena, in 1903. Two daughters, Annemarie and Käthe, resulted from this marriage. In 1925 Annemarie married Dr. Erich Hückel of Göttingen, who in Zurich was assistant to Professor Debye, and later became lecturer there.

He died in Göttingen on September 24, 1929.

Chemistry 1926

THE (THEODOR) SVEDBERG

«for his work on disperse systems»

Chemistry 1926

Presentation Speech by Professor H. G. Söderbaum, Secretary of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

The Academy of Sciences has decided to award the Nobel Prize in Chemistry for 1926 to The Svedberg, Professor of Physical Chemistry at the University of Uppsala, for his work on disperse systems.

Almost a hundred years ago, or more accurately in 1827, the English botanist Robert Brown discovered with the aid of an ordinary microscope that small parts of plants, e.g. pollen seeds, which are slurried in a liquid, are in a state of continuous, though fairly slow movement in different directions. A more detailed study of this phenomenon during the last few decades has led to extremely interesting results. By means of the ultramicroscope it has been possible to observe a similar, only much livelier movement with very much smaller particles of a colloidal nature. As we have recently heard, Einstein evolved a theory for this so-called Brownian movement which was then developed to a high degree by the now late Smoluchowski. According to these scientists, the movement arises through the impacts of the molecules of the liquid against the particles slurried in the liquid, provided that the latter are sufficiently small. Taking a crude analogy: if a fly or a gnat flies against an elephant, the elephant will not noticeably alter its position, but this can occur if the fly or gnat collides only with a bee.

The theory in question has been confirmed convincingly by experimental investigations of several colloid scientists among whom especially two of today's prize-winners, Perrin and Svedberg, have occupied and still occupy a leading position. Should it now be true that the movement of particles suspended in a liquid, which we can actually observe with the aid of our extremely highly magnifying instruments, can be explained only as a result of the movement of molecules beyond the limits of direct human vision, then this provides visual evidence for the real existence of molecules and consequently also for that of atoms, evidence which is all the more remarkable as not so long ago an influential school of scientists declared these particles of matter to be unreal fictions representing an obsolete viewpoint of science.

It is known that the opposition conducted by the colloid scientists so suc-

cessfully against this so-called energetic view has been continued by others who have gone much farther in that according to this view not only what we call matter, but also electricity occurs solely as particles of a definite size – the so-called electrons – and even that energy at all is regarded as bound to larger or smaller multiples of a smallest unit, the so-called elementary quantum.

If one has once become convinced of the existence of atoms and molecules, the question as to their real size is naturally – this hardly needs stressing – a question of the very greatest interest. Whereas it was formerly possible to calculate this size only roughly from the properties of gases and in connection with the theory applying to them, the position was now, as happens so often in the history of science, that almost simultaneously several new and considerably more precise methods for determining the natural constant in question appeared. Among these methods those based on colloid-chemical phenomena occupy a special position through their vividness and persuasive power, even though they may be for the time being slightly superseded by other methods in regard to accuracy. Also in this field Svedberg and the school of eminent scientists trained by him, Swedes as well as nationals from more or less distant countries, have achieved extremely valuable results. This has been done in several ways, among others, by determining the speed at which colloidal particles migrate by themselves, or diffuse in a liquid, or by measuring the distribution of such particles in a column of liquid, the latter according to a method proposed originally by Perrin.

In accordance with the theory for the movement of gas and liquid molecules which, as just indicated, has also been applied to colloidal particles, it is assumed that the mean value of the momentum of molecules or particles has a definite magnitude at each temperature, but that the speeds of the individual particles can vary within wide limits. If we now consider a very small volume fraction, the result is that, as Smoluchowski has calculated in detail, the number of particles present simultaneously within this volume can change from one moment to another. Svedberg and his collaborators have been able to confirm this extremely interesting conclusion that a « few-molecular » system having definite limits within a large volume of a material with a definite mean temperature may contain a varying number of particles, *partly* by counting the colloidal particles, *partly* in the case of solutions of radioactive substances by counting the number of so-called scintillations, i.e. light flashes, which radioactive particles produce when they impinge upon a screen coated with zinc sulphide.

With the last investigation, however, we have gone beyond the field of actual colloid chemistry, although the solution of a radioactive substance, e.g. polonium chloride, can naturally be called a disperse system, though more accurately it is molecular-disperse because the substance dissolved in the solvent occurs here as molecules, not as molecular aggregates, as is the case in a colloidal solution.

During the last few years Svedberg has completed an extremely ingenious invention, the so-called ultracentrifuge, which enables highly interesting investigations to be made also on such molecular-disperse systems. We know that when a slurry, an emulsion, is put into a rapidly rotating motion, its heavier constituents are thrown outwards in the direction of the periphery of the motion. This happens in the most used of all centrifuges, the milk separator, where the skimmed milk is pressed outwards whilst the lighter fat particles, the cream, accumulate inwards and can therefore be separated. Similarly in a solution, when centrifuging is sufficiently rapid, the molecules of the dissolved substance must accumulate outwards if they are considerably heavier than the molecules of the solvent. After overcoming exceptional experimental difficulties Svedberg succeeded in demonstrating this with the aid of an apparatus which allows the enormous speed of rotation of 40,000 revolutions per minute, and in which through a highly refined arrangement the progressive distribution of the particles within the extremely rapidly whirling solution can be observed and recorded photographically. The molecular weight of the dissolved material can be calculated from this distribution. This has already been done for certain proteins essential for organic life and for other substances allied to them. For example, the molecular weight of the red colouring agent of the blood, haemoglobin, has been determined as approximately 67,000 which assumes that there are in the region of 10,000 atoms in such a molecule.

In view of the fact that this year not less than three Nobel Prizes have been awarded for work in the field of colloid research, some people may ask whether this field really has a corresponding importance «for mankind».

By way of answer the following few remarks may be made.

Inorganic chemistry has revealed more and more cases where only a colloid-chemical approach was able to clarify the observed phenomena.

For physical chemistry colloids form a rich and rewarding field of research.

In organic chemistry we meet the perhaps most important colloids, the proteins and the polymeric carbohydrates, which cannot be studied without the aid of colloid research.

As all living matter is built up largely from organic colloids, the importance of colloid research for physiology and the medical sciences is obvious.

Finally, colloids play an important part in the various branches of chemical industry, such as in dyeing and tanning, in the cellulose, nitrocellulose, celluloid and textile industry, in rubber manufacture, in the pottery and cement industry, in the photographic industry, etc.

Professor Svedberg. With a feeling of sincere pleasure and justified pride the Academy of Sciences again sees itself able to recruit from the ranks of its own members the *corps d'élite* of researchers which has been set up by Alfred Nobel's legacy.

You have been able to accept on a previous occasion the assurance of the Academy on this together with its sincere congratulations.

In this festive hour we would now only add to this the hope that it may be made possible for you to carry out in your own country the important investigations which have already borne such fine fruit to the honour of Swedish research and which appear to be not less full of promise for the future.

The Svedberg

The ultracentrifuge

Nobel Lecture, May 19, 1927

Zsigmondy's pioneering ultramicroscopic research, which was awarded the 1925 Nobel Prize in Chemistry, confirmed that the colloidal solutions are a transitional sector between coarse suspensions and ordinary solutions. Zsigmondy's method in his own and other researchers' hands has helped us to a comprehensive knowledge of the size of colloidal particles. A reliable foundation for the study of colloids could not be laid until the ultramicroscope was constructed: the ultramicroscope showed that the colloids are disperse systems. Zsigmondy's method – although extremely valuable – does suffer from a twofold limitation however. Firstly, the ultramicroscope can be used to reveal the smallest particle sizes only with optically favourable material. The important lyophilic colloids in particular – for example ferric hydrate, silicic acid, protein, starch, cellulose, rubber – cannot as a rule be resolved in the ultramicroscope. Secondly, an ultramicroscopic study gives only very incomplete information concerning which different particle sizes are present in one and the same colloid. In other words, the distribution of the particle sizes cannot be determined. And it is precisely the lyophilic colloids and the finest grained amongst them that play the most important part in nature, and the distribution of their particle sizes is of the greatest interest to us.

In 1908 Perrin showed the applicability of Stokes' law to determination of particle sizes in coarse-grained disperse systems. In 1911 Estrup and the author showed the possibility of determining the distribution of the particle sizes by measuring the frictional resistance exerted against a single particle during its movement in the solution. The frictional resistance can be measured partly by dropping tests in the ultramicroscope and partly by measuring the Brownian movement.

In 1916 and the following year Odén succeeded, by using an automatically recording balance designed by himself, in preparing an elegant and reliable method of determining the particle-size distribution in coarsely disperse systems. His method is based on sedimentation in the gravitational field. It was an important step towards the solution of the general problem of determining the particle-size distribution in disperse systems in general.

It is, however, obvious that sedimentation analyses in the gravitational field can be carried out only on disperse systems consisting of relatively large particles of high specific gravity. To be able to study the actual colloids, the field of force must be increased many thousand times. This can be done by rotating the solution at high speed, i.e. by centrifugation. The only methods of observation applicable under such conditions are the optical. In 1922, Rinde and the author carried out tests with coarse-grained gold colloids in the gravitational field in order to try out the possibility of calculating the distribution of the particle-sizes optically by determining the changes of concentration in the solution during sedimentation. The changes of concentration were observed by means of light absorption in the solution. The method proved to be fully applicable. During the author's stay at Wisconsin University next year, Nichols and the author built a centrifuge to study the particle-size distribution. The concentration changes were observed by photographing the solution during rotation. The centrifugal force attained was only approximately 150 times gravity, so that it was possible to study only colloids of relatively low degree of dispersion. The particle-size of gold colloids down to ca. 20 $\mu\mu$ radius was determined with this apparatus. Next year (1924) Rinde and the author built a centrifuge which enabled a field of force up to approximately 7,000 times gravity to be produced (maximum speed about 12,000 r.p.m.). With this apparatus – which we called the ultracentrifuge – it was possible to determine particle-sizes and the distribution of particle-sizes down to those which would be invisible in the ultramicroscope. In 1925–1926, after means had been made available from the Andersson Medical Research Fund and from the Nobel Chemical Fund, Lysholm and the author built a new ultracentrifuge which permitted the study of solutions in fields of force of up to about 100,000 times gravity (maximum speed of revolution 42,000 r.p.m.). With this ultracentrifuge it is possible to cover the entire sector of the colloids down to the smallest particle sizes and even penetrate slightly into the actual molecular solutions. In so doing we reach a field of the very greatest theoretical and practical importance, the substances of high molecular weight, such as haemoglobin, protein, starch, etc. The limit of the possible has not yet been reached. The author hopes that with a new ultracentrifuge it will be possible to double the field of force and thus link up the centrifugation method analysis with conventional molecular-weight analysis carried out on solutions by determining boiling or freezing point.

A centrifugal field can be utilized in two different ways to determine particle size and molecular weight. Firstly, the sedimentation speed itself can be measured, and secondly it is possible to study the state of equilibrium – the so-called sedimentation equilibrium – which is assumed after a relatively long period of centrifugation. Both these methods link up with the classical examinations of the behaviour of coarsely disperse systems in the gravitational field which were carried out in 1908 and the next year by Perrin and his colleagues and which were awarded the Nobel Prize in Physics in 1926.

Let us imagine a small quantity of a highly disperse colloidal solution enclosed in a wedge-shaped cell rotating at an angular velocity ω about an axis coinciding with the apex of the wedge.

Each particle is subject to the action of two different and opposed forces: centrifugal force, which is $v(\varrho_p - \varrho)\omega^2 x$ and the frictional resistance which is $k.\mathrm{d}x/\mathrm{d}t$, where v is the particle volume, ϱ_p is the particle density, ϱ is the solvent density, x is the distance of the particle from the axis of rotation, k the coefficient of friction, and $\mathrm{d}x/\mathrm{d}t$ the speed of sedimentation. We therefore have:

$$v(\varrho_p - \varrho)\omega^2 x = k.\mathrm{d}x/\mathrm{d}t$$

If the particles can be regarded as being approximately spherical having radius r, then $v = 4/3\pi r^3$ and $k = 6\,\pi\eta r$, where η is the viscosity of the solvent. After substitution and integration:

$$r = \sqrt{\frac{9\,\eta \ln(x_2/x_1)}{2(\varrho_p - \varrho)\omega^2(t_2 - t_1)}}$$

If the substance has a high molecular weight, which will be denoted by M, the partial specific volume V, a molar coefficient of friction f and the coefficient of diffusion D, then we obtain instead the following equations

$$M(1 - V\varrho)\omega^2 x = f.\mathrm{d}x/\mathrm{d}t \quad \text{and} \quad f = RT/D$$

whence:

$$M = \frac{RT\,\mathrm{d}x/\mathrm{d}t}{D(1 - V\varrho)\omega^2 x}$$

or integrated:

$$M = \frac{RT \ln(x_2/x_1)}{D(1 - V\varrho)\omega^2(t_2 - t_1)}$$

If centrifugation is carried out for a sufficient length of time, equilibrium is finally assumed between sedimentation and diffusion. In that case, formulae for the particle volume and for the molecular weight can be derived partly kinetically and partly thermodynamically. For the volume v of the single particle we have:

$$v = \frac{2\,RT \ln(c_2/c_1)}{N(\varrho_p - \varrho)\omega^2(x_2 - x_1)(x_2 + x_1)}$$

and for the molecular weight:

$$M = \frac{2\,RT \ln(c_2/c_1)}{(1 - V\varrho)\omega^2(x_2 - x_1)(x_2 + x_1)}$$

where c_2 and c_1 denote the concentrations at the points x_2 and x_1.

Starting from the above formulae, it is possible to evolve methods of calculating the particle-size distribution. It would, however, take too long here to give an account of the mathematics used.

The centrifuge which was built by Rinde and the author and which permits observations in the field of force up to 7,000 times gravity has proved very suitable for the study of the sedimentation speed in reasonably highly disperse colloids and for a study of sedimentation equilibrium in extremely highly disperse colloids and crystalloids of high molecular weight. The solution or solutions to be studied is/are enclosed in plane parallel wedge-shaped rock crystal cells. Each test solution is covered with a layer of vacuum oil to prevent vaporization and convection currents originating therefrom. The cell holder together with the cells is placed in a rotor resting on the top of a vertical shaft mounted in a modified separator stand. To obtain a sufficiently constant temperature the step bearing of the vertical shaft is provided with a thermocouple-controlled cooling system, the rotor being surrounded by a hydrogen atmosphere. The friction in hydrogen is much less than in air, while in addition as a result of its high thermal conductivity hydrogen equal-

izes any temperature differences. The centrifuge housing is provided with two windows so that a beam of light can be applied through the solution during its rotation. Conditions at various times during centrifugation are determined by a camera. Photographic detection of the changes of concentration in the solution presupposes that the substance dissolved has absorption in the wavelength range of the illuminating light. Since only relatively few substances absorb in the visible part of the spectrum but most substances do so in the ultraviolet part, ultraviolet light in most cases has to be used for the photography. A suitable wavelength range can be isolated from a mercury-lamp radiation by means of filters containing chlorine and bromine.

A number of different concentrations of the same solution are photographed on the photographic plate bearing the exposures of the solution during centrifugation.

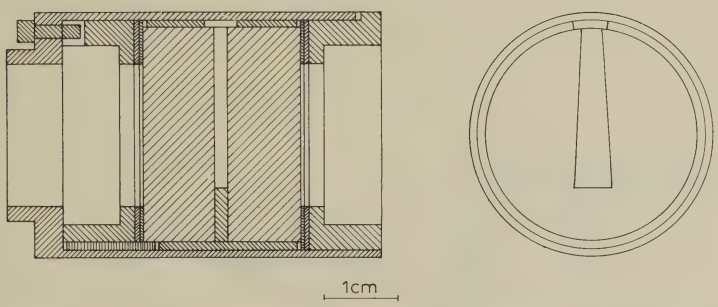


Fig. 1. Ultracentrifuge cell (longitudinal section and cross-section). The solution is enclosed in the plane-parallel wedge-shaped space between two glass or quartz plates.

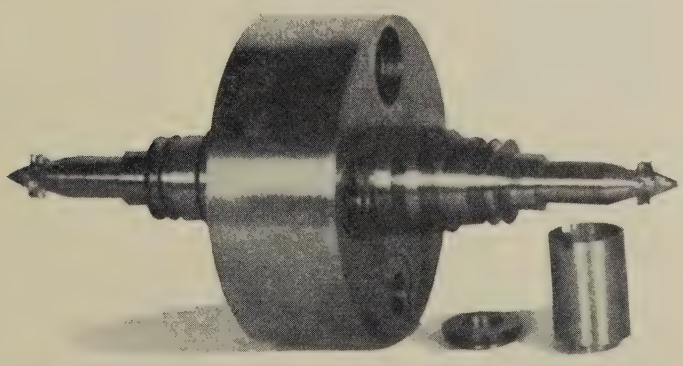


Fig. 2. The ultracentrifuge rotor with one of the cell cartridges removed.

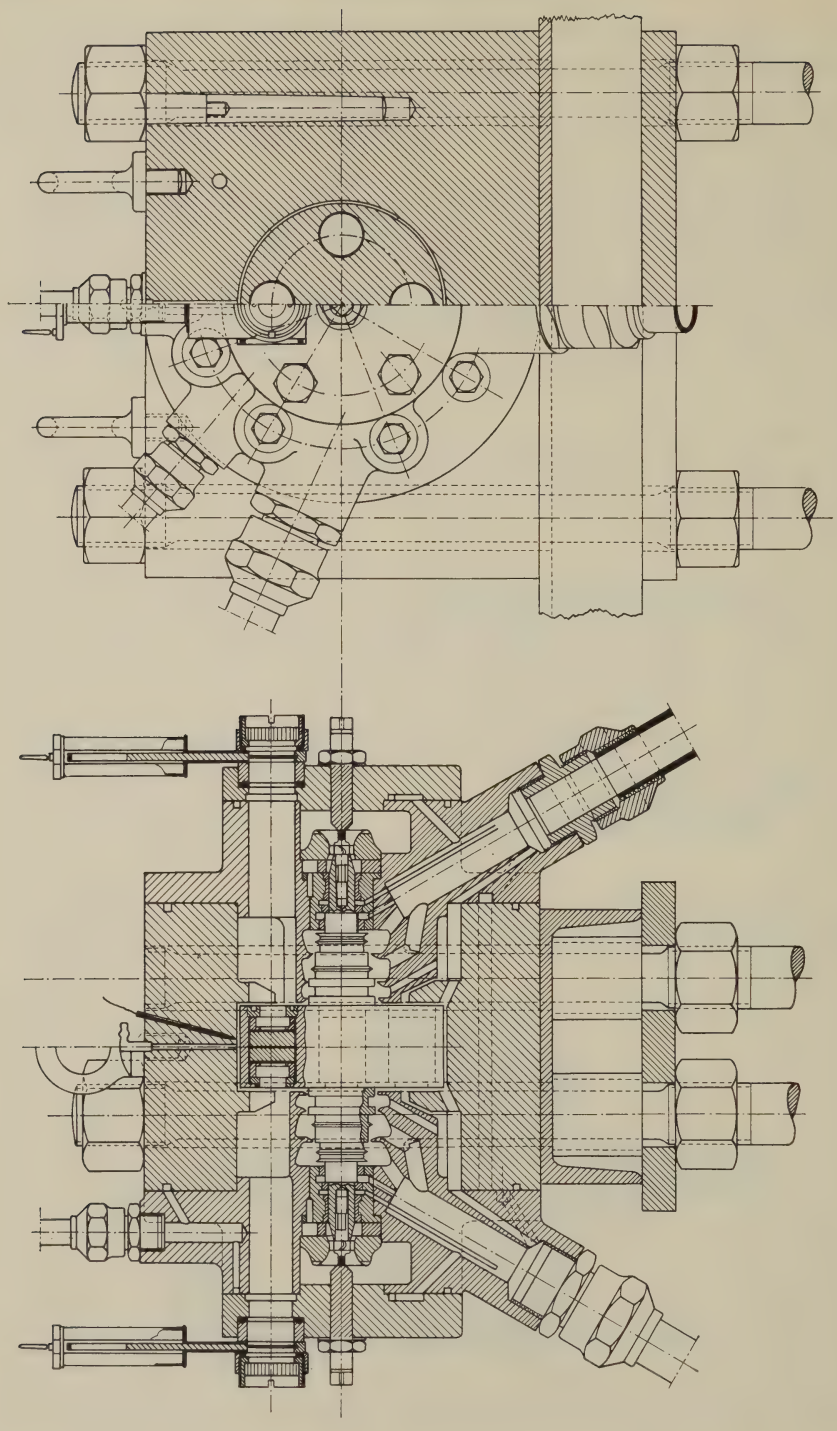


Fig. 3. The ultracentrifuge (longitudinal and cross-section).

After development, the plate is analysed by means of Siegbahn's self-recording microphotometer, and graphs are plotted to show the changes of concentration due to centrifugation.

As already stated, very strong fields of force are required for the study of the sedimentation speed in very highly disperse colloids. The ultracentrifuge which was built by Lysholm and the author in accordance with the

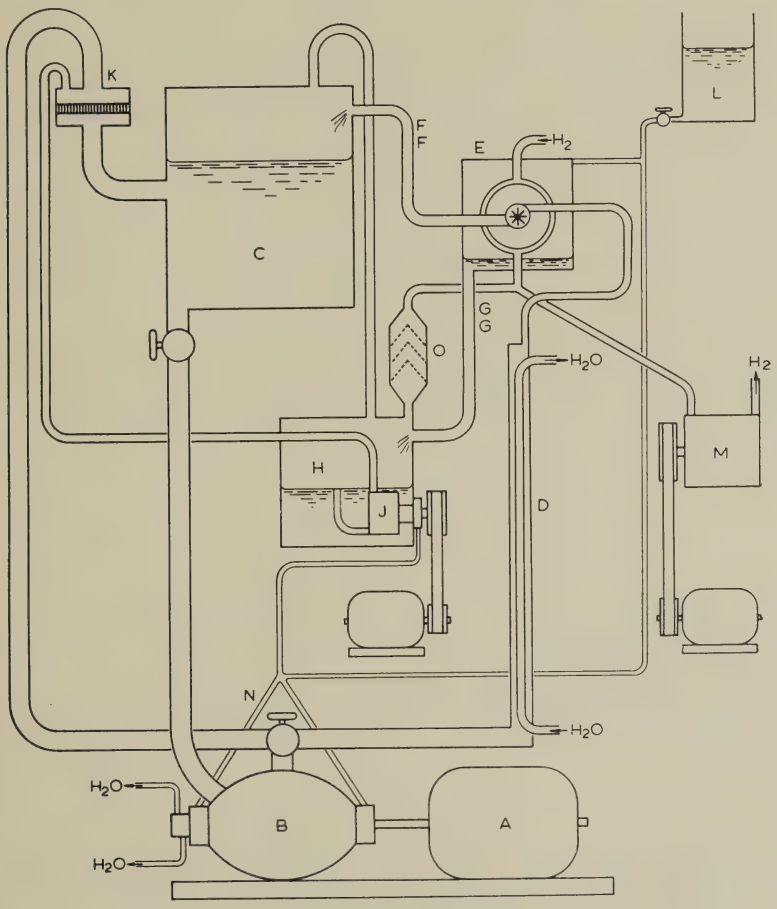


Fig. 4. The ultracentrifuge oil and hydrogen circulation system.

(*A*) electric motor	(*H*) oil tank
(*B*) oil pump	(*J*) oil pump
(*C*) oil tank	(*K*) oil filter
(*D*) oil cooler	(*L*) sealing oil tank
(*E*) ultracentrifuge	(*M*) vacuum pump
(*FF*) discharge pipe from turbines	(*N*) three-way cock
(*GG*) discharge pipe from bearings	(*O*) drip trap

theories of F. Ljungström, and which permits observations in fields up to above 100,000 times gravity, is suitable for such examination. The cells have a circular outer contour and are cemented into steel sleeves (Fig. 1). Four such sleeves are introduced into and screwed fast in the rotor (Fig. 2) of chrome-nickel steel. The rotor is mounted horizontally and is rotated by means of two small oil turbines. Fig. 3 gives an idea of the construction of the centrifuge.

To keep the heating within reasonable limits, the rotor should rotate in hydrogen at a pressure of about 15 mm Hg. This point represents an optimum. The reason for this is that the frictional work drops with the pressure, while the thermal conductivity and hence the coolability, is constant down to a fairly low pressure. The bearings are cooled by a vigorous flow of oil and thermocouples are used to control the temperature. Fig. 4 is a diagram of the oil and hydrogen circulation system. Fig. 5 is a diagram of the illumination and photographic systems. The methods of observation are similar to those used with the smaller centrifuge. The rotor speed is read from a stroboscopic tachometer (on the right in Fig. 5).

The above-described apparatus has hitherto been used for examination of

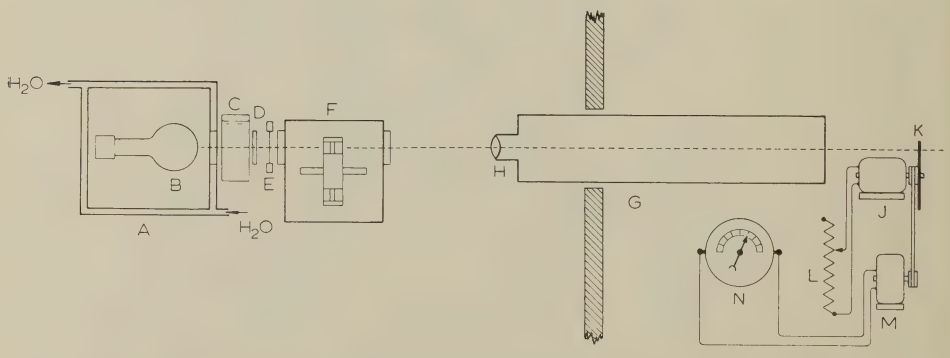


Fig. 5. Illumination and photographic system, together with stroboscopic tachometer, for the ultracentrifuge:

(*A*) water-cooled lamp housing
(*B*) lamp
(*C*) water filter
(*D*) light filter
(*E*) shutter
(*F*) ultracentrifuge
(*G*) camera
(*H*) objective
(*J*) motor
(*K*) stroboscopic disc
(*L*) resistor
(*M*) generator
(*N*) hot-wire ammeter graduated in r.p.m.

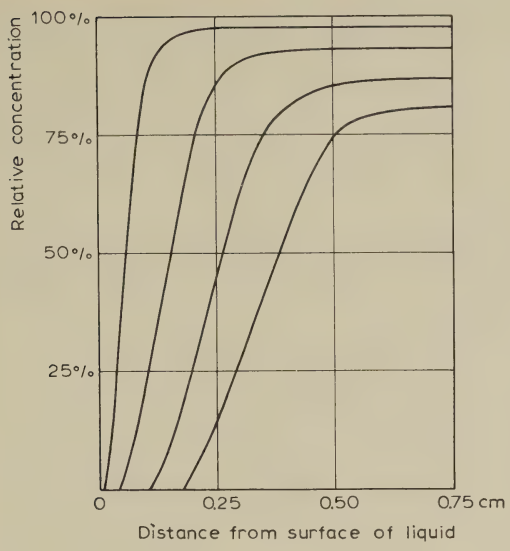


Fig. 6. Concentration distribution in a highly disperse gold colloid 5, 10, 15, 20 minutes after beginning of centrifugation; field of force 28,800 times gravity (according to H. Rinde).

synthetic inorganic colloids and for studies in connection with natural proteins.

Let us first consider the determination of the particle-size distribution in the gold colloids which are so well known from Zsigmondy's classic work. In this field Rinde has carried out exhaustive tests which have shown that these colloidal solutions are in no way as equal-grained as was previously thought. As an example we will choose the finest grained of all the gold colloids, the one reduced from chloroauric acid with phosphorus. Rinde has determined the particle distribution in such a solution partly by measuring the speed of sedimentation and partly by measuring the sedimentation equilibrium. Fig. 6 reproduces the concentration curves calculated from a series of exposures of such a colloid with sedimentation in a field 28,800 times gravity; the time between two exposures is 5 minutes.

Fig. 7 shows the distribution curve. As will be apparent from this curve, particles are present between 0.7 and 2.2 $\mu\mu$. The maximum is at about 1.5 $\mu\mu$. The sedimentation equilibrium for a similar gold colloid of rather coarser grain in a field 350 times gravity is reproduced diagrammatically in Fig. 8. Fig. 9 shows the distribution curve.

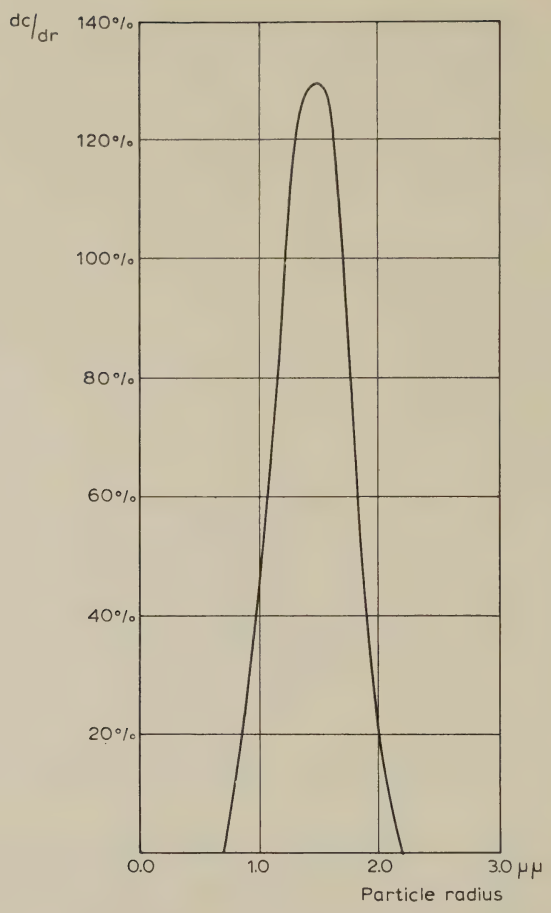


Fig. 7. The particle distribution in a highly disperse gold colloid calculated from the graph in Fig. 6 (according to H. Rinde).

Another field which during the last three years has been the object of centrifugation study at the Physical Chemistry Laboratory at Uppsala, is the proteins. In this case we determined the molecular weights partly by measuring the sedimentation equilibrium and partly by measuring the sedimentation speed. By means of the centrifugation method it is possible to determine molecular weights in very dilute solutions (hundredths of one per cent). This is important since many proteins have only low solubility. It is also possible in this way to determine whether a protein solution is or is not consistent in respect of molecular size. In cases where a protein has more than one light absorption band, it is also possible to test whether these

various bands relate to the same molecular weight. Thus Nichols has shown, in connection with carefully purified haemoglobin, that the light absorption in green, blue, and long-wave ultraviolet and in short-wave ultraviolet has as its vehicle a substance having a molecular weight in the region of 68,000.

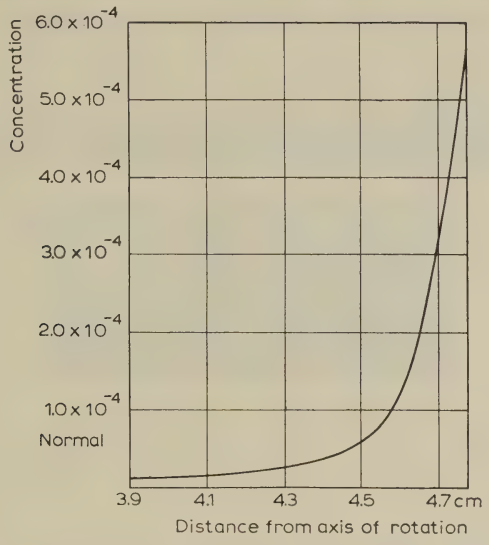


Fig. 8. Concentration distribution in a highly disperse gold colloid at sedimentation equilibrium in a field of force 350 times gravity (according to H. Rinde).

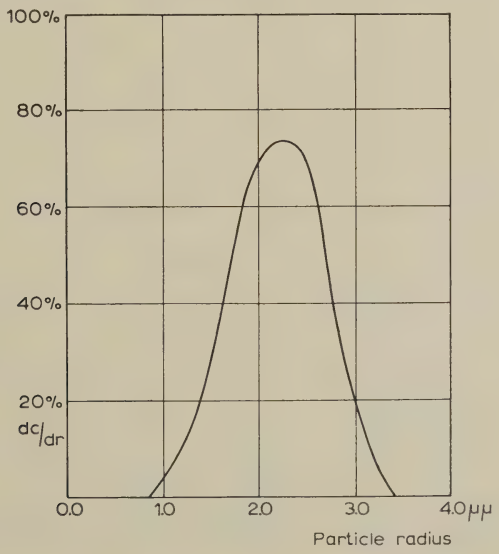


Fig. 9. The particle distribution in a highly disperse gold colloid, calculated from the graph in Fig. 8 (according to H. Rinde).

I give some data concerning the examination of haemoglobin. The study of the sedimentation equilibrium was carried out by Fåhraeus and the author (1924–1925) and was continued by Nichols (1926 and 1927); a study of the sedimentation speed was carried out by Nichols and the author (1926–1927). Fig. 10 is a series of exposures of a 0.9% solution of a compound of carbon

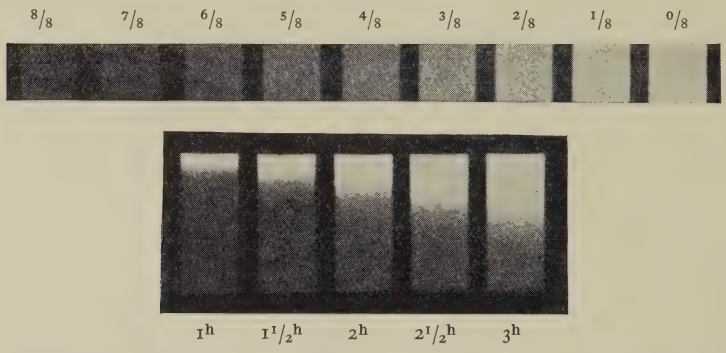


Fig. 10. Centrifugation of a solution of the compound of carbon monoxide and haemoglobin in a field of force 94,000 times gravity; time between exposures 1/2 hour; concentration scale at top.

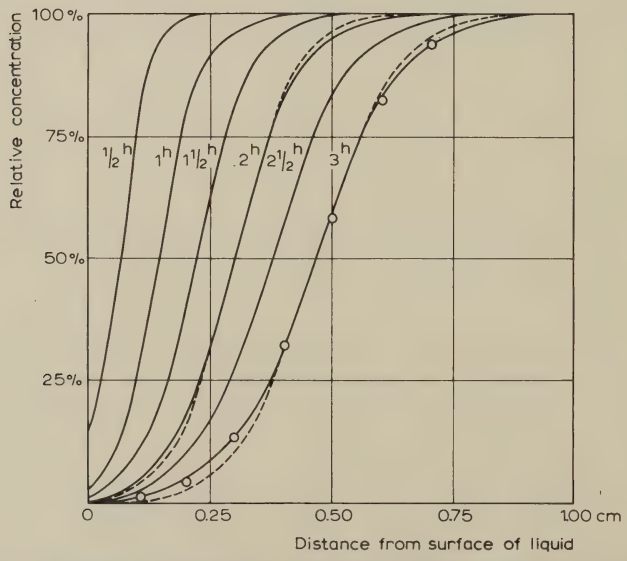


Fig. 11. The concentration distribution in a solution of the compound of carbon monoxide and haemoglobin 1/2, 1, 1 1/2, 2, 2 1/2 and 3 hours after the beginning of centrifugation; field 81,000 times gravity (curves are corrected for reduction in concentration due to wedge-shape of cell and field inhomogeneity).

monoxide and haemoglobin, taken 1, $1\frac{1}{2}$, 2, $2\frac{1}{2}$, and 3 hours after the beginning of centrifugation. The field of force was approximately 94,000 times gravity, the temperature 30°C. Table 1 shows two test series for determining the molecular weight of haemoglobin. The sedimentation equilibrium gave 67,870, the sedimentation speed 68,350. Fig. 11 shows the concentration curves from the last series (after correction for reduction of the concentration as a result of the wedge-shape of the cell and the inhomogeneity of the field of force). The solid lines represent the experimental values. The broken-line curves show the concentration distribution that would be expected if all the haemoglobin molecules (or particles) were of the same size. It will be clear that the deviation is insignificant. Calculations show that at least

Table 1. Haemoglobin.

Sedimentation equilibrium.

(*speed* = 8,708 r.p.m.; *centrifugation time* = 39 hours; $T = 293$; $\omega = 290.3\,\pi$; $V = 0.749$)

x_2 (*cm*)	x_1 (*cm*)	c_2 (%)	c_1 (%)	M
4.61	4.56	1.220	1.061	71,300
4.56	4.51	1.061	0.930	67,670
4.51	4.46	0.930	0.832	58,330
4.46	4.41	0.832	0.732	67,220
4.41	4.36	0.732	0.639	72,950
4.36	4.31	0.639	0.564	60,990
4.31	4.26	0.564	0.496	76,570
4.26	4.21	0.496	0.437	69,420
4.21	4.16	0.437	0.308	66,400
			Mean:	67,870

Sedimentation speed.

(*concentration* = 0.96%; $T = 303$; $V = 0.755$; $D = 0.070$)

Interval (*hours*)	Δx per ($\frac{1}{2}$*hour*)	*x-med.* (*cm*)	*speed* (*r.p.m.*)	$dx/dt : \omega^2 x$ (*cm/sec*)	M
0.5–1	0.074	4.525	39,300	5.36×10^{-13}	67,770
1 –1.5	0.078	4.601	39,400	5.44×10^{-13}	68,720
1.5–2	0.078	4.679	39,300	5.47×10^{-13}	69,090
2 –2.5	0.077	4.757	39,300	5.34×10^{-13}	67,450
2.5–3	0.080	4.840	39,200	5.44×10^{-13}	68,720
				Mean:	68,350

Table 2. Ovalbumin (salt-free).

Sedimentation equilibrium.

(*speed* = 10,700 r.p.m.; *centrifugation time* = 59.5 hours; $T = 288$; $\omega = 356.6\pi$; $V = 0.749$)

x_2 (*cm*)	x_1 (*cm*)	c_2 (%)	c_1 (%)	M
4.68	4.63	1.741	1.571	33,800
4.63	4.58	1.571	1.426	32,400
4.58	4.53	1.426	1.298	31,800
4.53	4.48	1.298	1.171	35,100
4.48	4.43	1.171	1.058	35,150
4.43	4.38	1.058	0.959	34,440
4.38	4.33	0.959	0.867	35,600
4.33	4.28	0.867	0.783	36,200
4.28	4.23	0.783	0.710	35,400
				Mean: 34,400

Ovalbumin (1% NaCl).

Sedimentation equilibrium.

(*speed* = 10,900 r.p.m.; *centrifugation time* = 41.5 hours; $T = 291.5$; $\omega = 363.3\pi$; $\varrho = 1.0077$; $V = 0.741$)

x_2 (*cm*)	x_1 (*cm*)	c_2 (%)	c_1 (%)	M	
				Found	*Calculated for 93.5% 34,000 + 6.5% 136,000*
4.68	4.63	1.822	1.586	44,000	44,900
4.63	4.58	1.586	1.393	41,900	42,400
4.58	4.53	1.393	1.230	40,500	40,250
4.53	4.48	1.230	1.092	39,200	38,650
4.48	4.43	1.092	0.973	38,400	37,400
4.43	4.38	0.973	0.875	35,600	36,650
4.38	4.33	0.875	0.788	35,750	35,900
4.33	4.28	0.788	0.708	36,950	35,450
4.28	3.23	0.708	0.641	34,800	35,100
4.23	4.18	0.641	0.580	35,000	34,750

80 to 90% of the haemoglobin in question consists of molecules of a weight of 68,000. More recent measurements by Nichols have given even higher percentages for this type of molecule. It is therefore clear that the protein haemoglobin is a substantially homogeneous chemical individual. By centri-

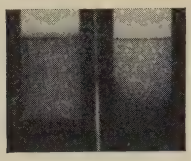
fugation of haemoglobin in various buffer solutions Nichols was able to prove that the molecular weight is independent of the degree of acidity, at least within the range of pH 6.0 – 9.0.

The following albuminoids were also studied: ovalbumin (Nichols and the author), phycocyanin and phycoerythrin (Lewis and the author), haemocyanin (Chirnoaga and the author). The examination of the first three is almost complete. The result has been that all must be regarded as substantially uniform chemical individuals. Fig. 12 is a photograph of the sedimentation equilibrium in an ovalbumin solution with an operative force of 5,800 times gravity. Fig. 13 is the concentration curve. Table 2 gives two test series with ovalbumin, one for a uniform material, and the other for a material containing a component of high molecular weight. Fig. 14 finally shows a centrifugation series with phycoerythrin. The field of force was 90,000 times gravity, the temperature 30°C and the time between exposures 20 minutes.

Table 3.

Substance	*Molecular weight*	*Method*	*Observer*
Ovalbumin (electrolyte-free)	34,500	equilibrium	Nichols and author 1926
Haemoglobin (electrolyte-free)	67,700	equilibrium	Fåhraeus and author 1925
Haemoglobin (electrolyte-free)	68,000	speed	Author 1926
Haemoglobin (buffer pH 6.2–7.7)	68,100	speed	Nichols 1927
Phycocyanin (buffer pH 7.0–7.9)	105,900	equilibrium	Lewis and author 1927
Phycocyanin (buffer pH 7.0)	105,000	speed	Lewis and author 1927
Phycoerythrin (buffer pH 5.0–6.8)	207,700	equilibrium	Lewis and author 1927
Phycoerythrin (buffer pH 5.0–6.8)	226,800*	speed	Lewis and author 1927

* Owing to the difficulty of measuring the speed of diffusion of the phycoerythrin exactly, this value is less accurate than the preceding value.



A B

Fig. 12. Centrifugation of an ovalbumin solution: (*A*) at beginnig of centrifugation; (*B*) after reaching sedimentation equilibrium; field of force 5,800 times gravity (according to J. B. Nichols).

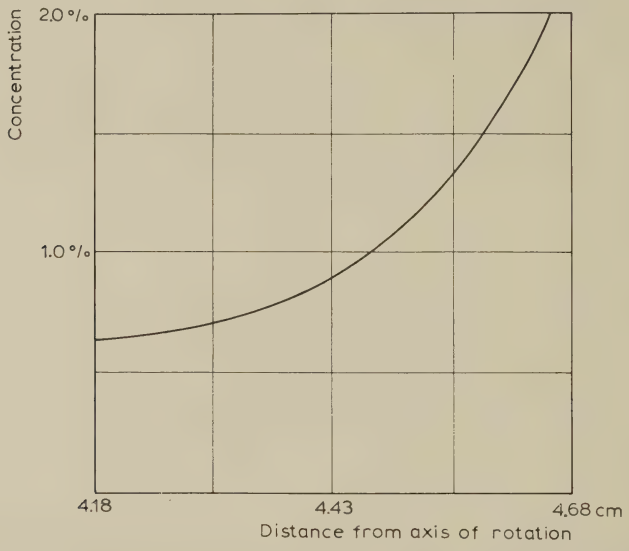


Fig. 13. The concentration distribution in an ovalbumin solution at sedimentation equilibrium in a field of force 5,800 times gravity (according to J. B. Nichols).

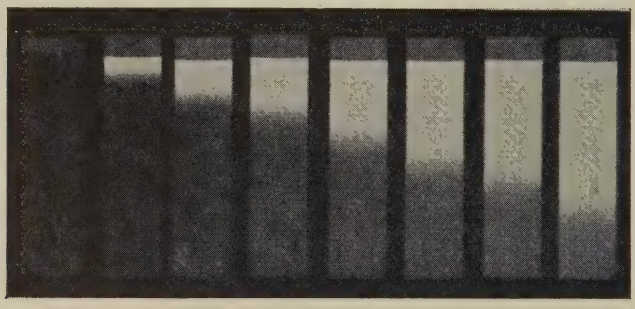


Fig. 14. Centrifugation of a phycoerythrin solution in a field of force 90,000 times gravity; time between exposures 20 minutes (according to N. B. Lewis).

Table 3 gives the molecular weights of the proteins hitherto studied by the centrifugation method. The values obtained by sedimentation equilibrium and sedimentation speed correspond to one another within the test error limits. It is interesting to note how the molecular weight of phycoerythrin is approximately twice the molecular weight of phycocyanin. These two proteins occur together in red algae (the material studied originates from a Swedish species of the genus Ceramium. According to analyses by Kylin (1910) and Kitasato (1925), their elementary composition is identical within the analysis error limits. According to the centrifugation examination carried out by Lewis, it is therefore probable that the main difference between them is that phycoerythrin has twice the molecular weight of phycocyanin. Phycoerythrin is red (strong absorption band in green), while phycocyanin is blue (strong absorption band in yellow). Since these two proteins are relatively difficultly soluble and they also contain no metallic constituents, it was impossible to determine or estimate their molecular weight in any way other than by centrifugation.

Examination of highly disperse colloids and other solutions of similar properties by centrifugation is still at its very beginning. The results obtained clearly show that in this way it will be possible gradually to collect a valuable fund of knowledge concerning such medicinally and technically important groups as the proteins, polymeric hydrocarbons (for example rubber), polymeric carbohydrates (for example starch, cellulose), etc.

Biography

Theodor (The) Svedberg was born at Fleräng, Valbo, in the county of Gävleborg, Sweden on August 30, 1884, as the son of Elias Svedberg, a works manager, and his wife, Augusta, *née* Alstermark. He attended the Köping School, the Örebro High School and Gothenburg Modern School, where he passed his student examination in December 1903, before matriculating and beginning his lifelong association with Uppsala University in January 1904. He gained his Bachelor of Arts degree in 1905, his Master's degree in 1907 and his Doctor of Philosophy in 1908.

Svedberg accepted a post as assistant in the Chemical Institute at Uppsala in 1905 and in 1907 he was given the additional position of lecturer in chemistry in the university. He obtained a special appointment in 1909 as lecturer and demonstrator of physical chemistry and in 1912 he was elected Professor of Physical Chemistry, University of Uppsala. He was made emeritus in 1949, since when he has been Director of the Gustaf Werner Institute for Nuclear Chemistry in the University.

Svedberg's work has mainly been concerned with colloids and macromolecular compounds. In his doctor's thesis *Studien zur Lehre von den kolloiden Lösungen* (1908), now considered as a classic, he described a new method of producing colloid particles and gave convincing evidence of the validity of the theory founded by Einstein and von Smoluchowski on the Brownian movements, thereby providing definite proof of the existence of molecules. With numerous collaborators he has studied the physical properties of colloids, such as their diffusion, light absorption, and sedimentation, from which could be concluded that the gas laws could be applied to disperse systems. For the study of sedimentation he constructed his well-known ultracentrifuge, where large molecules in solution, such as proteins, carbohydrates, and high polymers have been investigated. In the ultracentrifuge the large molecules are put under the influence of centrifugal forces up to about 10^6 gravity. The findings were related to molecular size and shape. He showed that the molecules of certain pure proteins are all of one size and demonstrated the use of the ultracentrifuge to show the presence of contaminants. Later, he turned

his attention to the problems of nuclear chemistry and radiation biology. He has also studied photographic processing, and assisted in photographing the famous *Codex argenteus* in colour, which made this source of the Gothic language available for research During the Second World War he worked out a method for making synthetic rubber.

Svedberg has contributed a large number of scientific papers to Swedish and foreign journals on colloid and high-molecular solutions, nuclear chemistry and radiation biology.

Among his publications the following books should be mentioned: *Die Methoden zur Herstellung kolloider Lösungen anorganischer Stoffe* (1909), *Die Existenz der Moleküle* (1912), *Colloid Chemistry* (1914; sec. enl. ed. with A. Tiselius 1928), *The Ultracentrifuge* (with K. O. Pedersen 1940; also in German). He has written several excellent popular books in Swedish, namely *Materien* (1912; sec. ed. 1919; also German ed. 1914), *Arbetets dekadens* (1915, 1920; German ed. 1923) and *Forskning och Industri* (1918).

He has been awarded the John Ericsson Medal (1942), the Berzelius Medal (1944), and the Medal of the Franklin Institute (1949). For his work on the disperse systems he received the Nobel Prize in 1925.

To extend his knowledge Svedberg has visited numerous laboratories in foreign countries and cities: Germany (1908), Holland and France (1912), Berlin (1913), Vienna (1916), London and Paris (1920), England and Denmark (1922), the United States and Canada (1922–1923).

He has been awarded honorary doctor's degrees in science and medicine, and, amongst many other academies and learned societies, he is a member of the Swedish Academy of Sciences, the Halle Academy, The Chemical Society (London), the Indian Academy of Science, the American Philosophical Society (Philadelphia), the New York Academy of Sciences, the Royal Society (London) and the National Academy of Science (Washington).

Svedberg has married four times: in 1909, Andrea Andreen, a medical graduate; in 1916, Jane Frodi; Ingrid Blomquist in 1938; and in 1948, Margit Hallén, M. A. He has twelve children, six sons and six daughters.

His hobbies are painting and botany.

Chemistry 1927 and 1928

HEINRICH OTTO WIELAND

[1927]

«for his investigations of the constitution of the bile acids and related substances»

ADOLF OTTO REINHOLD WINDAUS

[1928]

«for the services rendered through his research into the constitution of the sterols and their connection with the vitamins»

Chemistry 1927 and 1928

Presentation Speech by Professor H. G. Söderbaum, Secretary of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

We hear continually that today science, in particular natural science, is becoming increasingly more specialized, that scientists are delving deeper and deeper into specialized studies difficult to survey, that the deep stream of research is turning into ever-shallower brooks and channels, and that in this way the unity that exists between the different branches of science is in danger of being destroyed. Indeed, most people have wondered with some disquiet where this apparently unrestricted specialization will eventually lead. The answer to this question is that, while the question itself is completely justified, the disquiet is in most cases unjustified or at least unduly great.

A stage is reached sooner or later in the development of every natural science, when research, after dealing with problems of more general importance, has of necessity to apply itself to problems of detail of apparently more limited interest. It is simply that the continuous increase in scientific knowledge necessitates a corresponding continuous increase in the division of work. Many fields of science which could once be handled by a few or even one investigator, may only one generation later provide enough or more than enough work for whole hosts of students and their attendants. However, specialization is, or should be, not an end but a means. Even at the stage of the division of work, for the true investigator the end is, and will remain, that of determining the inner connection between the changing phenomena, and, depending on the extent to which this end is achieved, the special researches will gradually merge into greater units; the detail then ceases to be an isolated thing, more or less unimportant as regards the whole, but becomes a necessary link in a connected chain of knowledge.

The work which has been awarded Alfred Nobel's Chemistry Prizes this year by the Academy of Sciences, provides an instructive example of this process.

We are dealing here with several fields of work, which are separate from the start.

First we have biles. As is well-known, biles and hence their specific consti-

tuents, bile acids, are of major importance in the digestion process. Now these bile acids have been for almost a hundred years the object of active study by a large number of prominent investigators. In this way a large amount of material was accumulated from observations, but despite this, little was known concerning the connection between the various bile acids, and almost nothing concerning the details of their structure, when Wieland began his work in this field.

Then we have the cardiac poisons. Of animal cardiac poisons chemists were acquainted in particular with so-called bufotalin, which is present in the skin secretion of certain species of the toad genus *Bufo*. In therapeutics, on the other hand, vegetable cardiac poisons have long been used, especially those belonging to the glucoside group and obtained from species of the plant genera Digitalis and Strophantus. But the production of these substances in the pure state and the determination of the chemical relationships between them had long remained an unresolved problem.

The so-called sterols are also an extremely interesting group from the physiological viewpoint. They too occur both in vegetation and in animals. Most numerous are the vegetable sterols, the so-called phytosterols, but the best-known is certainly cholesterol, which occurs in the animal organism, and which was first found about 150 years ago in gall stones. This substance occurs not only in bile but also in the brain, in nerve substance, in the egg, in blood, and presumably in all cells. Thus we can conclude that it plays an extremely important part in the life process of man and the animals, just as the phytosterols play an extremely important part in the life process of plants. These sterols were however an isolated group for a long time. The difficulties associated with investigation of their chemical constitution were so great that it is only during the last few decades, above all through Windaus's investigations, that a clearer picture has been obtained thereof.

Finally, we come to a group of compounds which have only been known for a relatively short time, but which during this short time have attracted very considerable attention, both from chemists and from the public at large. Who today is unacquainted with vitamins, these mysterious substances which are of such immense significance for life, *vita*, itself and which have thus justifiably taken their name from it? But compared with those mentioned above, the difficulties which here confronted the investigator were far greater, and in most cases it had to be regarded as sufficient to characterize these substances on the basis of their physiological effects.

Thanks to the work which this year has been found before others worthy

of recognition through the award of the Nobel Prize in Chemistry, the inner connection between all these apparently isolated fields of research has been very strikingly demonstrated. Of course the way in which this took place can only be described very briefly here.

Wieland succeeded in producing from bile a saturated acid which can be regarded as the mother substance or parent acid of the bile acids, and which he studied and characterized in detail. When Windaus then produced this same parent acid, cholanic acid, from cholesterol by means of a complicated and very ingenious series of experiments, this indicated very clearly the close relationship between cholesterol and the bile acids. It should be pointed out in this connection that Wieland's investigations into bile acids themselves gave a deeper insight of the mechanism of the action of the bile in the resorption of food in the intestines.

But this is not all. As a result of patient and skilful work, Windaus succeeded in producing several of the digitalis glucosides and their components in the pure state. In this way it was shown that these vegetable cardiac poisons are directly related on the one hand to cholesterol and the bile acids, and on the other hand to the animal cardiac poison bufotoxin, which Wieland studied with great success.

Another sterol which Windaus has studied in detail, is ergosterol, which occurs partly in ergot and partly in yeast. The research carried out in recent years, in which Windaus himself has also played a leading part, has revealed the very important fact that, on being irradiated with ultraviolet light, this ergosterol assumes exactly the same properties as the antirachitic vitamin, « vitamin D », i.e. it will cure rachitis (rickets). For example, it has been found that 5 mg of irradiated ergosterol has the same action in this respect as 1 litre of good cod-liver oil. It can be considered proved, therefore, that ergosterol, or possibly a sterol the physiological effects of which correspond completely with those of ergosterol, constitutes the antirachitic provitamin, i.e. the mother substance of vitamin D.

All the investigations which we have had to summarize so briefly here, have one thing in common with each other. They were all designed to explain the internal structure of organic materials, their relationships with one another and their transitions into each other. For this reason they are of fundamental importance for our knowledge of a number of processes occurring both in the healthy and in the diseased organism, and therefore of greatest significance not only for chemistry as such, but also for its sister sciences, physiology and medicine. But in order to reach this vantage point of knowledge, where the

dividing walls separating the various special researches no longer obstruct vision, where the connection between extensive parts of organic chemistry can be surveyed and where in fact the fields of three main disciplines appear to connect and merge with each other – all this has taken years of hard, diligent, and resourceful work in the deep mines of detailed research. These are the researches which are to be rewarded here.

Professor Wieland. The decision of the Royal Academy of Sciences to award you the Nobel Prize in Chemistry for your work on bile acids and related substances, is only a just recognition of the solution of a problem which is without doubt one of the most difficult which organic chemistry has had to tackle.

The complex composition of the compounds investigated, the large number of atoms contained in the molecules of these compounds, the fact that the material was often very difficult to produce, even in small quantities, these were obstacles which could only be overcome with such striking success through a remarkable skill in experimentation and a rare capacity for finding new ways and means.

In gratitude for what you have achieved for science in this connection, and with hearty congratulations on your well-deserved distinction, the Academy asks you to accept the Nobel Prize in Chemistry for the year 1927 from the hands of his Majesty the King.

Professor Windaus. If the Royal Academy of Sciences had had only *one* Nobel Prize in Chemistry to award on this occasion, and had had to present it to one person, it would have been in a very difficult position.

For there is no doubt that your work on sterols, vegetable cardiac poisons and other closely related substances merits in the same high degree such an award as the work which we have just recognized.

Moreover, it is clear that your work and that of your colleague in Munich are so interrelated and supplement each other in such a way that it would have been extremely difficult to award the Prize to the one while passing over the other.

In addition, both researches display the same assiduity, the same remarkable capacity for overcoming even the greatest experimental difficulties, and the same lucidity in interpreting the results obtained, that it would obviously have been impossible to give precedence to one investigator over the other.

The fact that two Prizes were available for award this year, has fortunately

freed the Academy from this quandary. For this the Academy congratulates itself no less than you, and asks you now to take the last few steps which separate you from the external symbols of the Prize.

Heinrich O. Wieland

The chemistry of the bile acids

Nobel Lecture, December 12, 1928

Scientific chemistry occupied itself with the constituent substances of the bile at an early stage. L. Gmelin, Thénard and also Berzelius already did work on the acids present in bile, and several publications of the Liebig Laboratory in Giessen dealt with this subject. But it was only in 1848 that A. Strecker succeeded in isolating from ox-gall, the two most wide-spread acids, *taurocholic acid* and *glycocholic acid*, two conjugated substances of cholic acid $C_{24}H_{40}O_5$, condensed amide-like with taurine and glycine at the carboxyl group.

In 1886 Mylius discovered desoxycholic acid $C_{24}H_{40}O_4$ as a further constituent of hydrolysed bile; this second acid was isolated in the laboratory of Hammarsten in its natural form conjugated with taurine and glycine, from non-saponified bile. To this prominent Swedish investigator also goes the credit for the biologically important finding that it is cholic acid which predominates in the biles of numerous vertebrate animals investigated; this finding characterized the general physiological importance of cholic acid.

A third monocarboxylic acid $C_{24}H_{40}O_3$, lithocholic acid, poorer in oxygen, was discovered in 1911 by Hans Fischer in ox-gall stones, and afterwards proved to be an integral constituent of ox and human bile.

A year before Mylius, in 1885, Latschinoff had isolated an acid very similar in composition to desoxycholic acid which he called « choleic acid ». Later investigators took this as being an acid which is isomeric with desoxycholic acid, until in 1916 it could be shown that it consists of a remarkable addition product of desoxycholic acid and higher fatty acids (stearic acid, palmitic acid, oleic acid). This choleic acid contains 1 molecule of bound fatty acid per 8 molecules of desoxycholic acid, the fatty acid being bound so firmly that no dissociation into the constituents takes place during either salt formation or dissolution.

This observation prompted a comparison of the additive capacities of desoxycholic acid towards other substances, and the behaviour towards the series of fatty acids can be summarized by stating that these acids, right down to acetic acid, can unite in secondary-valence compounds of this type. Formic acid does not form « choleic acid », thus indicating that the chemical forces

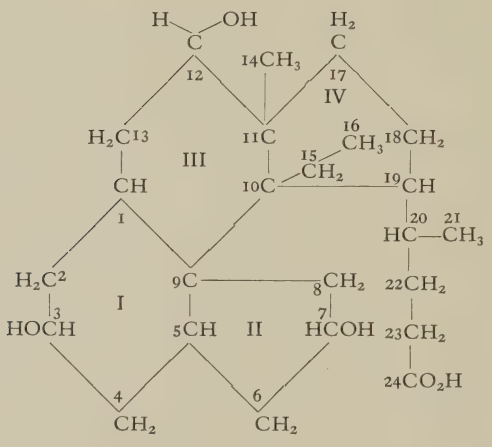
producing cohesion are to be found, not in the COOH groups, but in the saturated part of the fatty-acid molecule. H. Reinboldt has recently indicated that the choleic acids of the series being considered can be conceived as complex intercalation compounds of desoxycholic acid in the part of the fatty-acid molecule which has combining capacity. The fact that this capacity decreases with the number of carbon atoms in the fatty-acid molecule, indicates that one molecule of desoxycholic acid is held fast by the unit of each group $-CH_2 \cdot CH_2-$ or $-CH_2 \cdot CH_3$.

This intercalation capacity of desoxycholic acid is not restricted to the fatty acids. It is found in connection with all possible substances. Hydrocarbons, alcohols, esters, ethers, phenols, all unite with desoxycholic acid to form well-defined compounds containing as a rule only 2 molecules of desoxycholic acid. This generality of the addition capacity of desoxycholic acid has led to the use of the name « choleic acid » as a collective term.

The choleic acids containing neutral components insoluble in water, are absorbed by alkalies without decomposition taking place. On the other hand, the alkali salts of desoxycholic acid – and also those of cholic acid and of the conjugated cholic acid – will to a greater or a smaller extent absorb neutral substances insoluble in water. This applies, for example, in the case of fat, cholesterol, naphthalene, camphor, alkaloids such as strychnine, quinine, etc. A conclusion was drawn from this observation which is of importance with respect to the physiological function of the bile. It can be assumed that in the case of substances which are insoluble in water, transition into soluble choleinates enables diffusion through the cells of the intestinal wall. This would apply in particular to the fats and to cholesterol during the course of normal metabolism, but this « choleic acid principle » has been confirmed in medicine in other cases also. Its therapeutic use has led to the technical production of camphorcholeic acid, « cadechol »; I mention this in particular here, because but for this practical aspect of the discovery in question the tests to determine the constitution of the bile acids would have soon reached an impasse. For it would have been impossible to master, simply with the technical resources of a scientific laboratory, the quantity of initial material then required.

Turning now to a discussion of the problem of the chemical structure of bile acids, I should say first that in view of the time at my disposal it will be impossible to give an exact account of the various stages of the decomposition which was used as the main means of determining the constitution. I will try to describe in rough outline the chemical methods by means of which we got some insight into the constitution of the large and in many ways monot-

onous molecule. The problem is not very attractive from the experimental viewpoint. There is no nitrogen, which adds interest and variety to the treatment of alkaloids. Only carbon, hydrogen and a little oxygen, all in the traditional combination, which does not lead us to expect any surprising results. The task would appear to be a long and unspeakably wearisome trek through an arid desert of structure. True, the wanderer in this apparently so unattractive region, finds friendly landscapes at all stages of his journey, and the large quantity of substances bringing him nearer his goal, accumulates around him like dear companions, although, clothed in the plain garment of colourlessness, they do not stand out either in their appearance or in their properties.

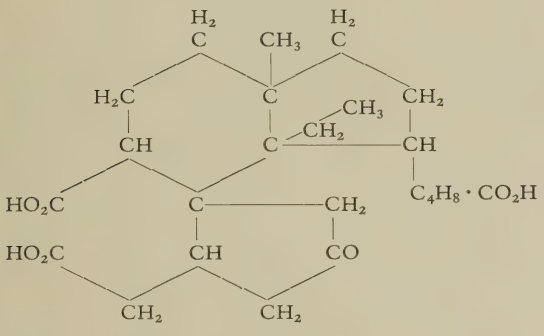


(I)
Cholic acid, $C_{24}H_{40}O_5$

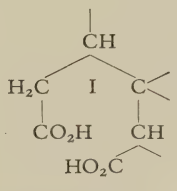
But the driving force, which steels the perseverance, lies in the problem itself. In order to get a comprehensive picture of the biological relationships in the wide field of chemically related natural substances which, in addition to the bile acids, includes the sterols, and very likely also the vegetable cardiac poisons from the group of saponins, the poisons from the skin secretions of toads, and probably also other important substances such as certain vitamins, we must above all be clear as to the fundamentals of their chemical structure.

My object, of briefly describing the extent to which the chemical nature of the bile-acid molecule has been determined, can best be achieved by basing my account on the formulae which so far appear to us to be the most likely ones. Formula (I) shows a saturated structure made up of four condensed

carbon rings and equipped with three branches. In a side chain is the carboxyl group determining the acid nature of the group. The three other oxygen atoms of the cholic acid are distributed in the molecule as alcoholic hydroxyl groups, in cholic acid they are located at the C-atoms 3, 7 and 12. In desoxycholic acid $C_{24}H_{40}O_4$ the OH-group at C_{12} is missing, and the single OH-group of lithocholic acid is bound at C_3. Windaus and I isolated a bile acid isomeric with desoxycholic acid $C_{24}H_{40}O_4$, at one and the same time, from the biles of various organisms, i.e. from that of the goose, of man and of the ox. This bile acid is called both chenodesoxycholic acid and anthropodesoxycholic acid. Though the two discoverers get on very well for the rest so far no agreement has been reached concerning a uniform nomenclature. In this acid the two alcoholic hydroxyl groups are at C_7 and C_{12}. Thus, it will be



(II)
Desoxybilianic acid, $C_{24}H_{36}O_7$



(III)
Iso-desoxybilianic acid, $C_{24}H_{36}O_7$

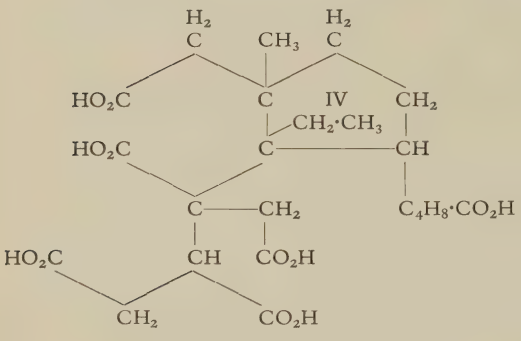
seen that the four most important bile acids are very closely related to each other, not only with respect to their fundamental structure, but also with respect to the distribution of their OH-groups.

Hammarsten was the first to show that the three OH-groups of cholic acid are of secondary-alcoholic nature, and already in 1881 he succeeded in converting cholic acid into dehydrocholic acid which contains six H-atoms less, through oxidation with chromium trioxide. All other bile acids behave analogously.

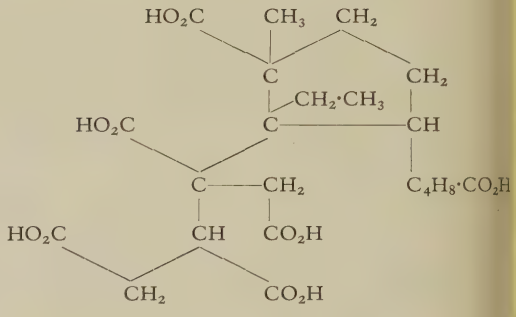
The first break-through into the molecule was achieved proceeding from desoxycholic acid, which can be opened up at the first ring by nitric acid via the stage of diketo acid. Here the two isomeric desoxybilianic acids form (Formulae (II) and (III)). The size of the ring was determined on the basis of Blanc's principle, according to which on thermal decomposition dicarboxylic

acids with 1,5-arrangement of the two CO_2H-groups turn into cyclic anhydrides, while those with 1,6- or 1,7-arrangement losing CO_2 and H_2O turn into cyclic ketones. The cyclic ketone produced in this way from desoxybilianic acid, was opened up into a hexacarboxylic acid via various intermediate products, in which only a single ring was retained and which was thus called solanellic acid (Formula (IV)). Through the thermal decomposition of this acid a new pentanone ring was produced from the split-up third ring, the further splitting-up of which led to biloidanic acid (V) $C_{22}H_{32}O_{12}$.

In this acid the paths of the decomposition from desoxycholic acid and cholic acid converged. Bilianic acid, the oxidation product of cholic acid corresponding to the desoxybilianic acid mentioned, can also be decomposed to form biloidanic acid via various intermediate products such as cilianic acid,



(IV)
Solanellic acid, $C_{23}H_{34}O_{12}$

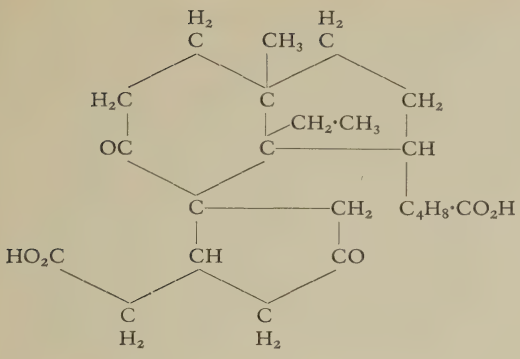


(V)
Biloidanic acid, $C_{22}H_{32}O_{12}$

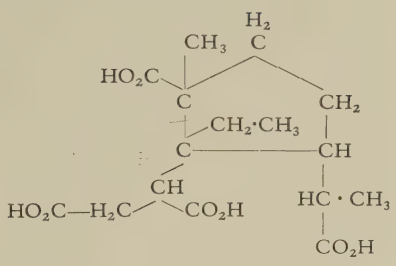
ciloidanic acid, which were explained with the help of the chemists M. Schenck and W. Borsche. But all attempts to penetrate into the last ring of the molecule proceeding from biloidanic acid, were unsuccessful.

As seen above, in the two experiments described only two carbon atoms were clearly removed from the large molecule. The principle followed up till then, that of proceeding step by step, had to be abandoned for the object of the investigation to be attained within a reasonable time. This measure was justified by the fact that the structure of the molecule this side of the unknown fourth ring was known in all its details.

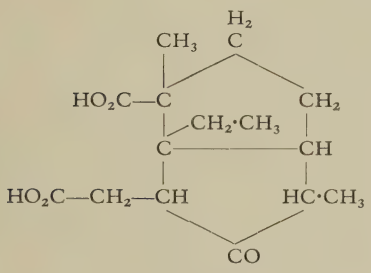
On oxidation of the pyrodesoxybilianic acid with permanganate, a diketodicarboxylic acid (VI) had been isolated as an intermediate product; this was turned into a tetracarboxylic acid $C_{16}H_{24}O_8$ by means of nitric-sulphuric acid in a smooth reaction. Here seven carbon atoms are broken off, including, for reasons to do with the closed part of the molecule, two from the side



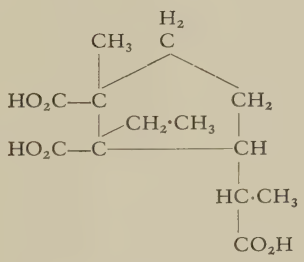
(VI)
Diketo-dicarboxylic acid, $C_{23}H_{34}O_6$



(VII)
Tetracarboxylic acid, $C_{16}H_{24}O_8$



(VIII)
Keto-dicarboxylic acid, $C_{15}H_{22}O_5$

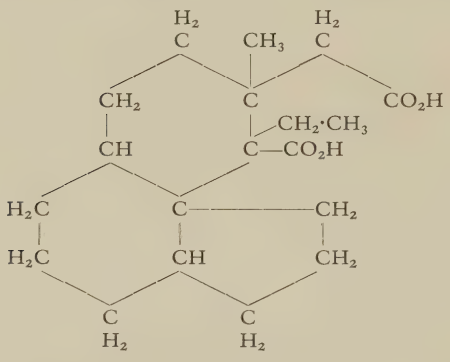


(IX)
Tricarboxylic acid, $C_{13}H_{20}O_6$

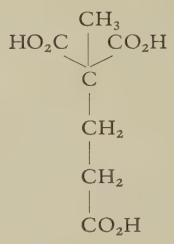
chain, which is thus shortened by two C-atoms. Formula (VII) is proved for this tetracarboxylic acid, because on thermal decomposition, it turns into a keto-dicarboxylic acid $C_{15}H_{22}O_5$ (VIII) (unfortunately the yield is very low), and this can then be turned into a tricarboxylic acid $C_{13}H_{20}O_6$ (IX).

Since week-long operations yield only 5 g of this acid from 1 kg of desoxycholic acid, in determining the constitution the attack was transferred to another point of the molecule, viz., the side chain, about which some knowledge was already available from the work of Windaus on cholesterol. We were able to assume that a methylated C-atom is located in the γ-arrangement to the COOH group. This side of the molecule had also to be opened by the oxidation decomposition method. Proceeding from the ester of cholanic acid, $C_{24}H_{40}O_2$, the parent substance of the whole group, we turned this by means of the Grignard reaction into diphenylated carbinol, which was then submitted to oxidation by chromic acid. In this way one C-atom after another was split off. The fourth split away with the third, indicating that it was replaced by a CH_3-group. Proceeding from the acid $C_{20}H_{32}O_2$, the monot-

ony of this procedure underwent a welcome change. On oxidizing the corresponding tertiary carbinol, we came across a dicarboxylic acid $C_{19}H_{30}O_4$, etiobilianic acid (X). Thus the opening of the fourth ring was achieved and the number of links in it was found by thermal decomposition according to Blanc, which gave an anhydride and not a cyclic ketone. The fourth ring was thus recognized to be a fifthring, and from the formation of the etiobilianic acid it could be concluded that in addition to the C-atom carrying the side chain, there is a methylene group. The relationships between the side chain and ring II (lactone formation with the OH-group at C_7, condensation with the CO-group of the dehydro acids) indicate that the position of the side chain is as shown in the formulae.



(X)
Etiobilianic acid, $C_{19}H_{30}O_4$



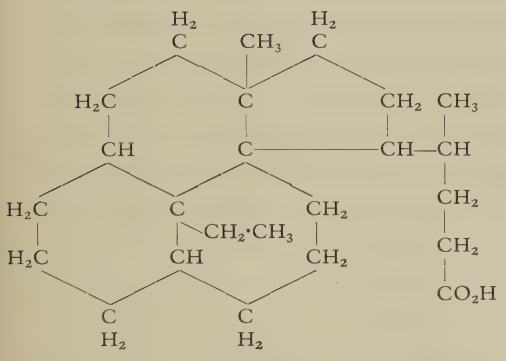
(XI)
α-Methylglutaric-α-carboxylic acid, $C_7H_{10}O_6$

If we assume that the third ring is attached to the two C-atoms 10 and 11 of ring IV, then only three C-atoms are now unaffected by the structural investigation. We can make a positive statement about one of these C-atoms. On oxidation of the diketo-dicarboxylic acid $C_{23}H_{34}O_6$ mentioned above, in addition to the tetracarboxylic acid $C_{16}H_{24}O_8$ a small amount of a malonic acid was isolated, which is closely related to α-methylglutaric acid. It has the Formula (XI). The methyl group found here cannot be identical with that which we encountered in the side chain; it must be attached to C_{11}, which is the only way of explaining the occurrence of a malonic acid. But we are still unable to decide whether the other three C-atoms of the tricarboxylic acid $C_7H_{10}O_6$ come from ring III or ring IV. Thus, the formula for bile acid corresponding to the present status of our knowledge is still hypothetical, in so far as the location of the last two carbon atoms has not been determined very precisely. At present there are simply indications that the proposed ar-

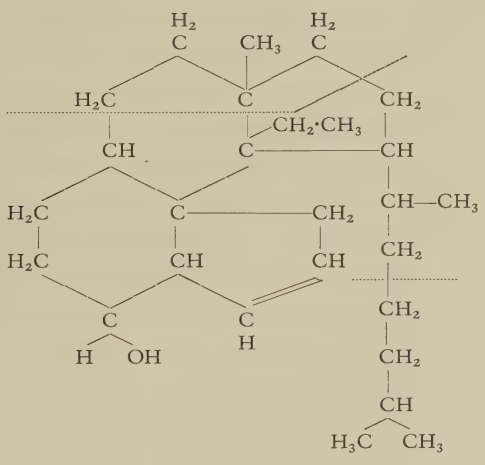
rangement with an ethyl group at C_{10}, has advantages over one with an ethyl group at C_{18} or a division into two methyl groups at the points mentioned.

But the most recent investigations, which I cannot go into in detail here, introduce Formula (XII) into the range of the discussion.

This, then, characterizes in rough terms the status of our knowledge of the chemical constitution of the bile-acid molecule. Despite the unsuccessful attempts of physiologists at producing experimentally the transformation of cholesterol into cholic acid in the animal organism, it must be assumed that the vegetable sterols provided by food are transformed by the cell according



(XII)
Cholanic acid, $C_{24}H_{40}O_2$



(XIII)
Cholesterol, $C_{27}H_{46}O$

to the system of the decomposition reaction carried out by Windaus on pseudocholestane. When we attempt to get a picture of the mechanism by which the plant cell builds up the sterols, reference to the formula of cholesterol (XIII) shows that its molecule consists of three isoprene groups and a residue of twelve rectilinearly-bound carbon atoms. Since the plant can easily convert carbohydrates into fats, it may perhaps be assumed that an intermediate stage of this transformation is employed for condensation with the terpene-type component. The rings are formed either through intramolecular dehydrations or through splitting off water.

Relationships with natural amino acids are found in the existence of the bile acids conjugated with glycine and taurine. They are even more pronounced in the poison of native toads, which is without doubt clearly related

to the bile acids. In this, the so-called bufotoxin, we find a molecule of suberic acid esterified by an OH-group of the fundamental structure $C_{24}H_{34}O_5$; the other carboxyl of the suberic acid is bound like an amide with arginine. A second hydroxyl carries the acetyl group. If the chain of the suberylarginine is split-off hydrolytically, the strong cardiac poison bufotalin remains, the acetic ester of a trioxy-lactone $C_{24}H_{34}O_5$. It can be assumed that here the typical carboxyl group of the bile-acid molecule has been lactonized to give the tertiary γ-arrangement. No accurate check has yet been carried out on the structural association between bile acids and toad poison. Here the difficulties of preparing the material are particularly great.

When the last puzzles of our constitution problems have been solved, we can expect as usual the synthesis of the compounds. In cholanic acid there are seven asymmetric carbon atoms, and in cholic acid there are ten; as yet no procedure has been developed for the experimental production of the peculiar bonding of the numerous rings. While I acknowledge that it is the duty of the organic analyst to carry out syntheses such as have been carried out so excellently in the investigation of the coloured components of the colouring matter of blood, I must decidedly repudiate this in the field being discussed. I am fully conscious, however, of the duty to follow the course that has been embarked upon right to the end.

Biography

Heinrich Otto Wieland was born as the son of Württemberger parents, Dr. Theodor Wieland and Elise Blom, on June 4, 1877, in Pforzheim where his father was a pharmaceutical chemist. He studied at the Universities of Munich, Berlin and Stuttgart, and then returned to the Baeyer Laboratory in Munich where, in 1901, he received his doctorate under Johannes Thiele. In Munich, where he had chosen to make his home, he received in 1904 the *venia legendi* and in 1913 a senior lectureship in the University Chemical Laboratory. In 1917 he transferred his activities to the Technical College nearby as a full Professor. From 1917–1918 he was busy at the Kaiser Wilhelm Institute in Berlin-Dahlem working on Defence. In 1921 he accepted a call to Freiburg and in 1925 returned to Munich at Willstätter's request to succeed him in his Chair in the University of Munich. For twenty-seven years the destiny of the Munich laboratory lay in his hands.

Wieland's scientific work, recorded in four hundred publications, covers a wide field in the realm of Organic Chemistry and Biochemistry.

For several decades Wieland's attention was claimed by the organic nitrogenous compounds. His brilliant studies of the reaction of nitrogen oxides with olefins and aromatics, the clarification of furoxanes as well as the classical experiments with fulminic acid and its polymerization may be chosen as examples. In the same connection, Wieland succeeded in the first production of stable organic nitrogen radicals, of diphenyl nitrogen and its N-oxide. The proof of short-lived radicals in solution reactions involved him in an extensive series of experiments whose importance for the modern development of organic radical chemistry can hardly be overestimated.

In later years Wieland was entirely devoted to the chemistry of natural substances. His contributions to the clarification of the structure of morphine and strychnine, the constitution and synthesis of the lobelia alkaloid and the research into the curare alkaloid were masterpieces. Work on the poisonous agent in the «death cap» mushroom led to the isolation of the crystalline cyclopeptides phalloidine and amanitine; work on the pigment of butterflies led to the discovery of the biologically important class of pterin compounds.

The publications which began in 1912 on the subject of bile acids culminated in 1932 in the clarification of the carbon framework of the steroids, whose general importance in Nature Wieland recognized.

Much of Wieland's life work was occupied by the investigations into the oxidation processes in living cells, which enabled him to recognize dehydrogenation as a universal oxidation principle in Nature. This work restored the unity of Organic Chemistry and Biochemistry which had been lost since the time of Liebig.

It is not surprising that Wieland was accorded all the honours that the scientific world has to offer. He was a member of the great learned societies of the world, he was awarded a Nobel Prize in 1927, he received the Order of Merit and the Otto Hahn Prize, and for twenty years he was Editor of *Justus Liebigs Annalen der Chemie*. Wieland's great school is evidence of his importance as an academic teacher.

In an age of increasing specialization, Wieland was among the last of those who were able to enjoy an encyclopaedic knowledge of the whole of Chemistry.

In 1908, he married Josephine Bartmann of Munich. They had three sons, Wolfgang, a doctor of pharmaceutical chemistry; Theodor, professor of chemistry in the University of Frankfurt; and Otto, professor of medicine in the University of Munich, and one daughter, Eva, who is married to Professor Feodor Lynen, professor of biochemistry in the University of Munich, Nobel Laureate in Physiology or Medicine, 1964.

The great scholar's life was ruled by hard work, but also by love and kindness both to his pupils and to his family; it ended shortly after his 80th birthday, on August 5, 1957, in Starnberg.

Adolf Windaus

Constitution of sterols and their connection with other substances occurring in nature

Nobel Lecture, December 12, 1928

The exceptional distinction which the Royal Academy of Sciences has accorded to my work «on the sterols and their relationship to other natural products» places upon me the honour and duty of giving an account of my research to this assembly.

The sterols are nitrogen-free secondary alcohols of high molecular weight which contain in their molecules a number of alicyclic systems. A sharp distinction between the sterols and other naturally occurring hydroaromatic alcohols is not always possible.

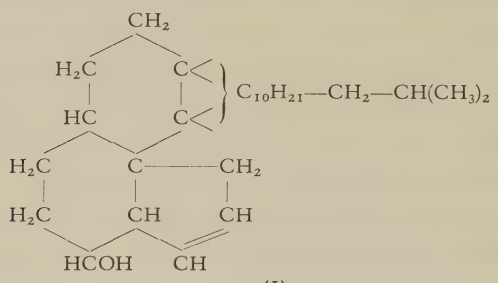
The sterols are widely distributed in the animal, vegetable, and fungal kingdoms. The best-known sterol is *cholesterol*, which was first discovered in human gall-stones, and received the name cholesterol because of its presence in bile. It is a mono-unsaturated alcohol, with the formula $C_{27}H_{46}O$, found in all the higher animals, partly as free alcohol, and partly as fatty acid esters; it is present in particularly large quantities in the brain and the adrenal cortex and as a pathological deposit in gall-stones, sclerotic aorta, and other organs affected by fatty degeneration. The fluctuations of cholesterol content to which human blood serum is subject are very surprising; during pregnancy the quantity is considerably increased, while during most infectious diseases it is noticeably reduced.

In the lower animals, the insects, the echinodermata, and the sponges a number of sterols occur which are collectively known, together with cholesterol, as *zoosterols*. The majority have the same formula as cholesterol and are very similar to it; only the spongosterol, discovered by Henze in *Suberites domuncula*, appears not to be an unsaturated compound, and is more clearly differentiated from cholesterol than the other zoosterols.

In the vegetable kingdom, too, wherever they have been sought, sterols have always been found. They are grouped together as phytosterols and occur in plants partly as free alcohols and partly as glucosides. The most widely distributed are phytosterols (sitosterols) which have the same formula as cholesterol; there are, however, also phytosterols which contain not one, but

two double bonds, and saturated phytosterols are also frequently mixed in small quantities with unsaturated ones. Somewhat apart from the typical sterols are sterol-like alcohols, which are differentiated from sitosterols by the number of carbon atoms, and, finally, those which contain more than one hydroxyl group. The variety of the phytosterols is therefore great, and it is noticable that, despite this great variety, animal cholesterol has never been discovered among the numerous plant sterols.

Specific sterols are also found in fungi and are classified as *mycosterols*. *Ergosterol* was first isolated from ergot by Tanret, and it is also found in numerous other fungi and especially in yeast. It has the formula $C_{27}H_{42}O$ and contains, in contrast to cholesterol and sitosterol, not merely one, but three double bonds. It is particularly significant that this ergosterol is mixed in very small



(I)
Cholesterol

quantities (about 1/10%) with all zoosterols and phytosterols. In addition to ergosterol still other sterols are found in fungi – *zymosterol* in yeast, and *fungisterol* in ergot. There are certainly many more.

It is surprising that in *bacteria*, as far as they have been examined, no sterols occur. Panzer noted their absence from tuberculous and diphtheria bacilli, and I can confirm this result for the tubercule bacilli, as I have worked on several kilogrammes of these. I have shown by physiological means that ergosterol does not occur even in traces in tubercle wax.

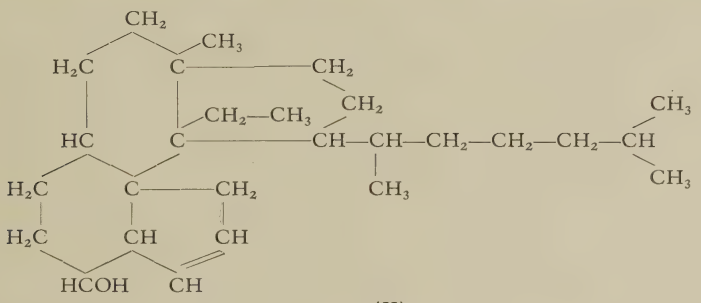
Chemically by far the most thoroughly examined is the sterol of the higher animals, cholesterol. The laborious and protracted investigation of its constitution has shown that it probably possesses the structure (I). According to Wieland's research this formula may be resolved into the complete structural formula (II). This formula is very complicated and has no similarity to the formulae of sugar, fatty acids, or the amino acids which occur in protein.

The synthesis of such a substance appears to the chemist particularly diffi-

cult, and up till now I have not dared to attempt it, as success is extremely improbable. Furthermore, the majority of physiologists have not been inclined to believe the animal organism capable of such a synthesis, for it is known that other, seemingly simpler, syntheses – e.g. that of tyrosine and tryptophan – have not succeeded in the animal organism.

If the human and animal organism were really not in a position to produce cholesterol from other constituents, then the cholesterol of the higher animals, the carnivores and herbivores, would necessarily originate in their food. But as the herbivore does not receive cholesterol but phytosterol in its food, it must possess the ability to absorb the phytosterol of its vegetable nourishment and to convert it to cholesterol.

To test this assumption Schönheimer carried out experiments on rabbits



(II)
Cholesterol

in the Institute of Pathology in Freiburg. He found 96.9% of the ingested sitosterol (0.2 g per day) in the excrement, and concluded from this that sitosterol is not absorbed by the intestinal canal of the rabbit. There can therefore be no question of the herbivore using the phytosterol in its food to form the cholesterol of its body substance. On the contrary, it must be in the position to form cholesterol from other components of its nourishment.

Whether or not mycosterols behave like phytosterols still remains to be accurately established. On the other hand, it is known that cholesterol, which is so extremely similar to sitosterol in its physical and chemical properties, behaves physiologically in quite a different manner. It is absorbed by both herbivores and carnivores and particularly easily when bile salts are available in abundance. Schönheimer found only 50% of the ingested cholesterol (0.2 g per day) in the excrement of rabbits. Furthermore, the cholesterol content of the blood is greatly increased after feeding with cholesterol, and it is noticeable that after long periods of feeding with cholesterol symptoms of disease

appear in the animal. Mice, rats, and cats accumulate cholesterol, which is introduced with the food, principally in the liver, so that the cholesterol content of this organ can increase to more than five times normal, and a severe anisotropic fatty degeneration of the liver becomes apparent. If small doses of cholesterol are fed to rabbits deposits occur at first only in the intima of the blood vessel, which is the organ most sensitive to cholesterol in the rabbit. This observation is of very great interest, for according to Aschoff a disease pattern arises at this point which is identical with that of arteriosclerosis in man. The hypothesis of a genetic connection between ingested cholesterol and arteriosclerosis in man thus cannot be dismissed. Since phytosterols, which cannot be absorbed, bring about no such symptoms, it should be investigated whether or not true arteriosclerosis presents itself in societies which are truly vegetarian (abstaining also from milk and eggs).

Although the animal thus is in a position to absorb cholesterol from its food with the aid of bile salts, nevertheless not even the carnivore is dependent on this cholesterol introduced from outside. As Beumer has demonstrated, puppies fed on a diet deficient in cholesterol exhibit after four weeks an increase of cholesterol which is twenty times greater than the amount given in the food. Particularly painstaking have been the investigations of Randles and Knudson into the question of a cholesterol synthesis. They have succeeded in maintaining white rats on a diet completely free of sterols, on the basis of the discovery that pulverized alfalfa, on extraction with cold ether, relinquishes its sterols completely, but retains enough vitamins for the maintenance of rats. The scientists mentioned reached the incontestable conclusion that the cholesterol content of fully-grown rats fed on a diet free of cholesterol is many times greater than the cholesterol content of new-born rats. The only possible explanation for this is that the organism of the rat is capable of forming cholesterol from substances which are different from the sterols and other substances soluble in ether.

There is thus in the animal organism a cholesterol synthesis, and the synthetic capabilities of the animal have been gravely underestimated here, as in many other cases.

In the animal organism some substances are found which according to their formulae could be related to cholesterol. These are *isocholesterol*, *coprosterol*, the *bile acids*, and *bufotoxins*.

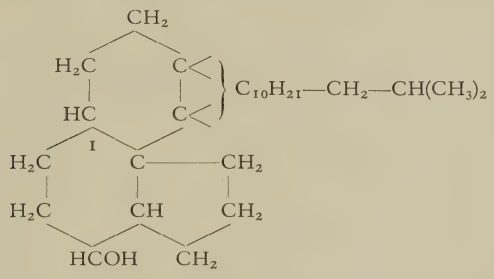
About *isocholesterol*, which occurs in the lanolin of sheep, only very little is known.

Coprosterol is found in the faeces of carnivores; it must be formed from

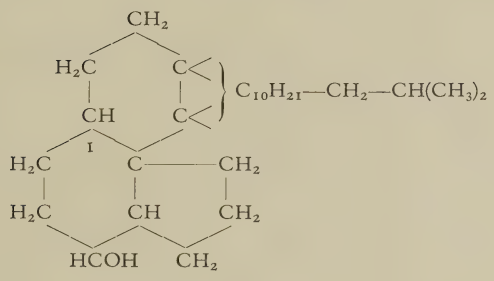
cholesterol through the action of intestinal bacteria. However, it has remarkably not been possible outside the intestinal canal to change cholesterol into coprosterol by the use of putrefactive bacteria.

Coprosterol is according to its formula a dihydrosterol, but it is not identical with the normal dihydrocholesterol which, according to Willstätter's research, arises from the catalytic hydrogenation of cholesterol, and which is likewise found in small quantities in faeces.

According to the long-continued research which I have been engaged on,



Dihydrocholesterol (III)

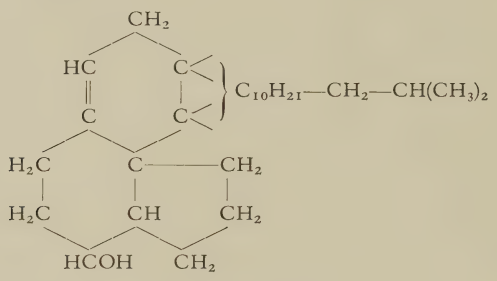


Coprosterol

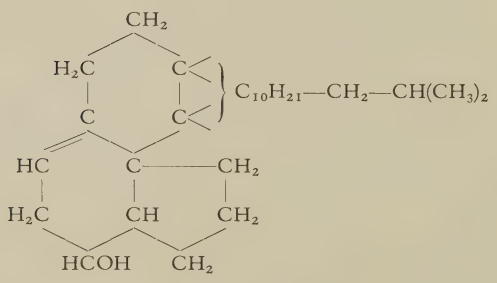
dihydrocholesterol and coprosterol appear to differ from each other by the position of the substituents in the carbon atom 1 of the carbon-skeleton shown in formulae (III). An artificial conversion of cholesterol into coprosterol can be achieved by means of changing cholesterol into an isomer with hydrochloric acid. This has been named *allocholesterol*, and probably possesses one of the two formulae (IV). From the hydrogenation of allocholesterol undertaken in a neutral solution coprosterol is formed, the only or almost the only product of the hydrogenation. Allocholesterol has not yet been found in the animal organism, but it is nevertheless quite possible that it is in fact present there. For it is very easily converted into ordinary cholesterol under the most diverse circumstances; and in the reactions which are involved in the isolation

of cholesterol from animal matter, this transformation would certainly take place.

Using coprosterol as a starting-point, an important conversion from the sterols to *bile acids* has also been discovered. The familiar bile acids (formulae (V)) derive from an acid $C_{24}H_{40}O_2$, Wieland's *cholanic acid*; that is, they contain 3 carbon atoms less than cholesterol and coprosterol. These three carbon atoms may be separated out of coprosterol as acetone via the corresponding hydrocarbon, coprostane, by using an oxidizing agent; and in this way



or

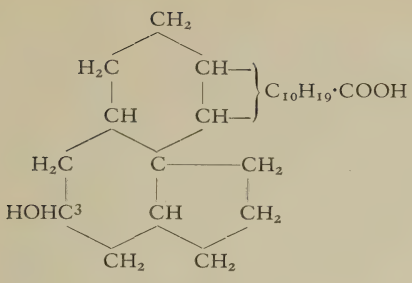


Allocholesterol (IV)

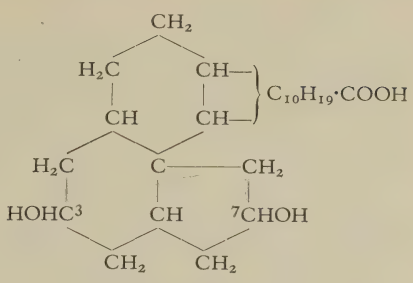
Wieland's cholanic acid is arrived at, as formula (VI) indicates. Moreover, some time ago Wieland carried out the appropriate synthesis, and succeeded in returning from cholanic acid to coprostane.

The chemical connection between cholesterol and bile acids is completely clarified by this, and it is interesting that bile acids also derive not from normal cholesterol, or rather dihydrocholesterol, but allocholesterol, or coprosterol.

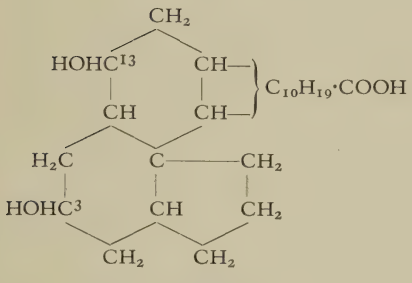
Does this close chemical relationship correspond to a biological connection? That is, are the bile acids produced through the degradation of cholesterol within the organism as well? Upon this question Thannhauser and his colleagues have recently been engaged, and have produced important results. First they demonstrated on a dog with a gall-bladder fistula that the cholesterol ingested with the food is by no means sufficient as a source for the bile



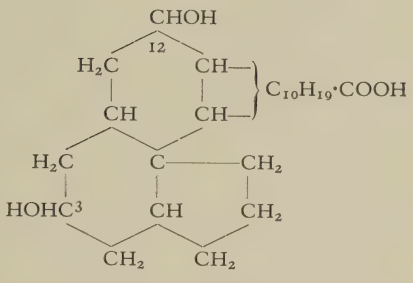
Lithocholic acid



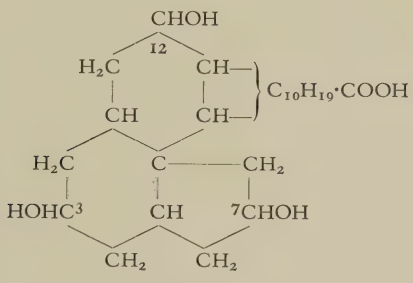
Desoxycholic acid



Hyodesoxycholic acid

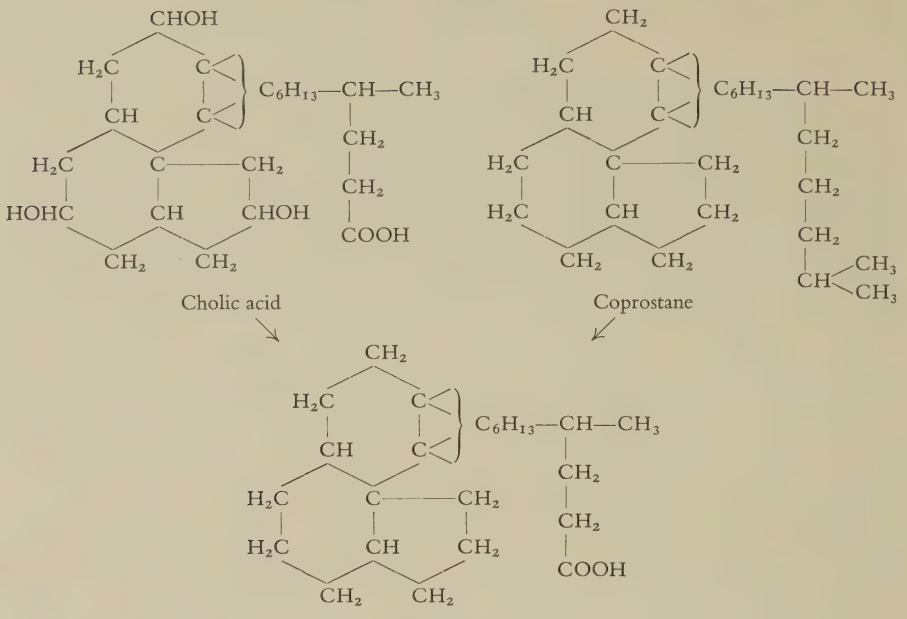


Chenodesoxycholic acid



Cholic acid (V)

acids. It is, moreover, never transformed into bile acid in the animal organism even in the case of intravenous injection; on the contrary, isomeric *allocholesterol* and *coprosterol* bring about an increase of the bile acids corresponding to the quantity injected. This discovery is of very great significance; it shows first of all that the animal organism is not capable of forming allocholesterol from cholesterol. It does, however, make it probable that allocholesterol plays an important part in the intermediate metabolism. Perhaps things are so placed that the organism synthesizes, not the cholesterol, but the allocholesterol, and that this represents the parent substance of coprosterol as well as of the bile acids. Perhaps, the sterol secreted in the intestinal canal, which



(VI)

is hydrogenated to coprosterol, is not cholesterol at all, but the unstable allocholesterol, and perhaps the formation of gall-stones in bile depends on the fact that the easily soluble allocholesterol is prematurely transformed into the difficultly soluble cholesterol.

At any rate the attempt to prepare coprosterol with putrefactive bacteria outside the intestinal canal should be repeated on allocholesterol.

In place of the bile acids of the type of oxycholanic acid, there is found in the bile of sharks a *scymnol sulphuric acid*, which is an acid ester of scymnol, a polyvalent alcohol of the formula $C_{27}H_{46}O_5$. The assumption suggests itself that this scymnol is a multiply hydroxylated cholesterol, but that has not yet been established; and likewise it is very probable that the basic component of bufotoxin, *bufotalan*, is an oxylactone of the formula $C_{24}H_{38}O_3$, closely related to the bile acids.

What, then, is the biological role of cholesterol itself? Many attempts have been made to solve this question. A number of scientists place in the foreground the physical – especially the colloid-chemical – properties of cholesterol, and they point to the ability of cholesterol to emulsify fat, and to its importance for the permeability of the cell. The conditions prevailing here still badly need explanation.

We are well informed about *one* biological property of cholesterol, but it is uncertain whether this is of any significance for the organism. It concerns the ability of cholesterol to detoxicate a series of haemolytic poisons, and to increase the resistance of the red blood corpuscles.

It was Ransom who first discovered that blood serum is in a position to detoxicate haemolytic poisons like, for example, saponin, and that the cholesterol present in the blood serum is the effective factor in this. Later, it was found that cholesterol forms easily characterized and easily crystallized additive compounds with a number of saponins, especially with the digitalis-saponins, and that these additive compounds are not toxic. The detoxication thus depends on the formation of complex compounds. Some of the complex compounds are so difficultly soluble that they make an exact evaluation of cholesterol possible; a separation of the cholesterol ester from cholesterol may be carried out also with the help of the digitonin method.

In recent years a fact which has come to excite the interest of chemists and physiologists above all is the connection between the sterols and the antirachitic vitamin. The antirachitic vitamin is present in comparatively large quantities in the unsaponifiable portion of fish-liver oils, which is an effective remedy for rickets. The German physician Huldschinsky was as far as I know the first to discover that as well as fish-liver oils, irradiation with ultraviolet light constitutes a remedy for rickets. Two American scientists, Hess and Steenbock, then discovered independently of each other that it is not even necessary to irradiate the diseased organism, but that it is sufficient to irradiate the food with which it is to be nourished. These scientists, and at about the same time two English scientists, Rosenheim and Webster in London, next established that the substance which can be activated is situated in the unsaponifiable part of the nutriment, and is identical with the sterols.

It was at first believed that all sterols – animal, vegetable, and fungal sterols – would be activated by ultraviolet light; but it then became apparent from physical measurements (Heilbron, Pohl) and from biological experiments (Rosenheim and Webster, Hess and Windaus), that cholesterol and sitosterol contain in traces an admixture which renders activation possible, and that cholesterol may comparatively easily be freed from this contamination. Proof was then successfully given that this admixture is identical with the ergosterol of fungi, or, to put it more circumspectly, manifests exactly the same absorption spectrum and exactly the same physiological behaviour as ergosterol.

The biological effect of ergosterol is extremely surprising. A fortnight's admixture of 1/20,000 mg daily of irradiated ergosterol to «rachitogenic»

nutriment is sufficient to protect a rat from rickets. Irradiated ergosterol is more than 100,000 times more effective than good fish-liver oil. All the scientists who have tested this result are in a position to confirm its accuracy. Opinions are still divided only about whether ergosterol is the only substance which is transformed into antirachitic vitamin under irradiation, or whether there are other precursors.

Jendrassik and Kemenyffi in Budapest take the view that the capacity of cholesterol for being activated should be attributed for by far the greater part to an admixture of ergosterol, but that cholesterol itself is self-activating, however small this effect may be. And Bills and his co-workers have likewise reported that by painstaking refinement the susceptibility of cholesterol to activation can indeed be depressed to a thirtieth part, but there would remain constant. The view that cholesterol itself may be activated does not hold good. It is certainly true that when cholesterol is refined with blood-charcoal or by way of dibromide a certain susceptibility remains; but this depends on the

Fig. 1. Absorption coefficient. Ergosterol 0.04% in ether.

exceptional difficulty of separating – or rather, destroying – the last remnants of ergosterol. By repeated purification of cholesterol via crystallized allocholesterol, a cholesterol was successfully obtained the activity of which is at least 300,000 times less than that of ergosterol; and Kon and Steenbock have by repeated oxidation of cholesterol with potassium permanganate similarly obtained a completely *inactive cholesterol*. Other substances which are similar in structure to ergosterol – *zymosterol*, *cholatrienic acid methyl ester*, and *digitaligenin* – cannot be activated. The assertion that digitaligenin might be activated was propounded by Holtz and myself.

Thus up till now the only precursor of vitamin D in existence is ergosterol.

For the transformation of ergosterol into antirachitic vitamin, ultraviolet light of a wavelength of between 253 and 302 mμ is suitable; light of a longer wavelength than 313 mμ or shorter than 248 mμ has no definite effect. This result is easily understood if we consider the absorption spectrum of ergosterol (Fig. 1).

Activation was still obtained at $-183°$. Some 700–1000 erg are necessary to produce the quantity of vitamin D which has an immediate physiological effect (about 1/50,000 mg). If irradiation continues too long the vitamin D is destroyed.

Besides ultraviolet light, cathode rays are also suitable for the activation of ergosterol. Knudson and Coolidge obtained the transformation when they caused high-tension cathode rays of 100,000 to 350,000 volts to act upon the sterol for 30 seconds. After 900 seconds, however, the vitamin had disintegrated. Whether α-rays are effective appears not yet to have been attempted, but it is indeed very probable. With so-called dark electrical discharge or with X-rays we have obtained no activation of ergosterol.

We also attempted, with sensitizers, to make ergosterol sensitive to long-wave light. In this certain light reactions were successfully produced; but they are principally of a nature different from that of the ultraviolet reaction, and do not lead to vitamin D.

If ergosterol and eosin are irradiated with visible light, a stoichiometrical reaction takes place between the ergosterol and the eosin, by which eosin hydrogenates and ergosterol is dehydrated under the formation of a pinacol, $C_{54}H_{82}O_2$. If all the eosin is hydrogenated the reaction is brought to a standstill. If ergosterol and eosin are treated with visible light in the presence of oxygen, the eosin acts as a catalyst and straight away a crystallized ergosterol-peroxide arises. But both products are ineffective against rickets; thus, no vitamin formation has been observed using visible light.

Equally small has been our success so far in obtaining the transformation of ergosterol into vitamin D by chemical means. It is, however, not apparent why this method should not still be successful. On the contrary, a whole series of scientists believe that vitamin D can be produced in the vital functions even without ultraviolet light. Thus Völtz indicated that grass seedlings cultivated in darkness, derived from vitamin-free seeds of *Lolium perenne*, contained a small quantity of antirachitic protective material. These experiments need re-examination. Opinions are also divided over whether the abundance of vitamin D in cod-liver oil originates in the nutriment of the cod, which is rich in vitamins, or whether the vitamin is formed synthetically within the organism.

What, then, takes place when ergosterol is irradiated? Of course there is a chemical alteration along with the physiological activation; this announces its presence in that, when irradiated, ergosterol, which, like all sterols, yields with digitonin an insoluble additive compound, gradually loses its precipitability through digitonin. The course of the chemical transformation is even easier to follow in the alteration of optical rotation. In the usual solvents ergosterol manifests a strong laevorotation which under irradiation slowly diminishes and finally is transformed into a weak dextrorotation As an example the curve for ligroin may be given (Fig. 2).

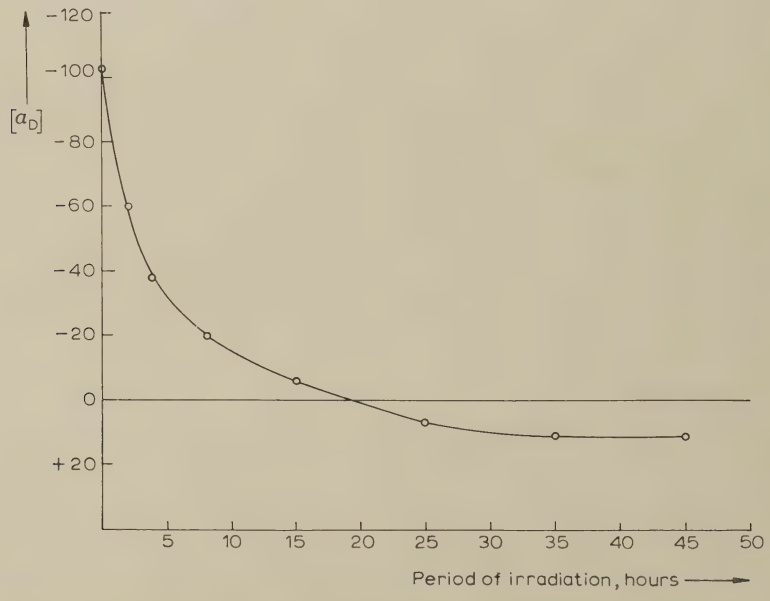


Fig. 2. Irradiation of ergosterol in normal benzine (Kahlbaum) 0.35 % solution. Period of irradiation in hours.

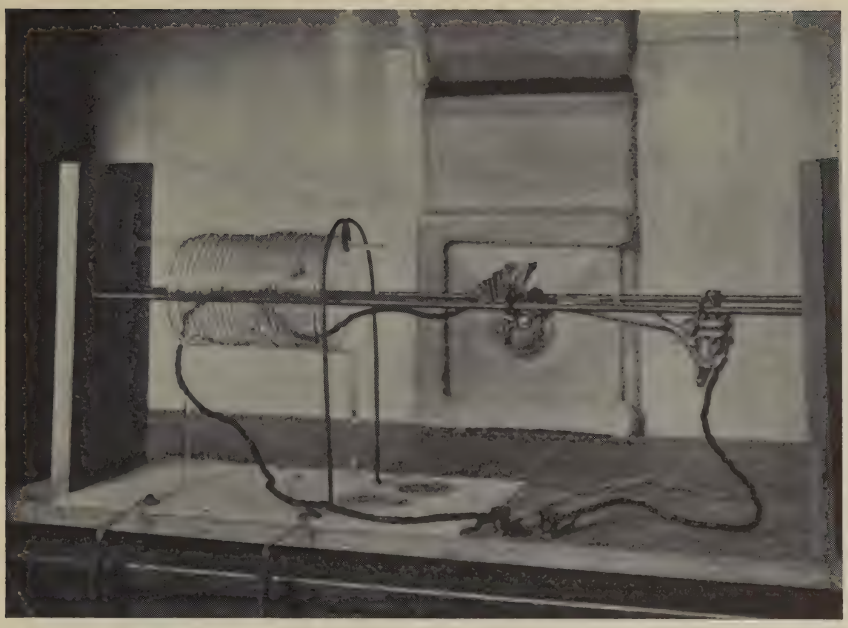


Fig. 3.

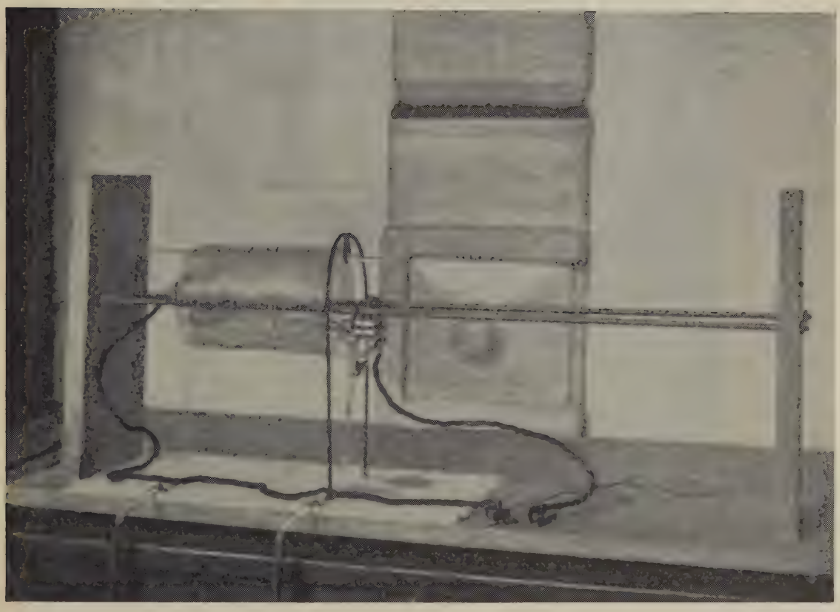


Fig. 4.

At the same time as the alteration of the optical rotation, an alteration of the ultraviolet absorption spectrum and a remarkable increase in solubility ensue. In order to obtain from irradiation values which may be easily reproduced, it is necessary not only to exclude oxygen completely, which is very difficult, but also to irradiate all parts of the solution as far as possible uniformly. First of all we attempted the activation by putting a quartz-spiral around the mercury lamp and sending through it a 0.25 % alcoholic solution of ergosterol under nitrogen pressure (Figs. 3 and 4).

Later we heated the etherized solution of ergosterol to boiling point in a double-walled quartz vessel, and led through it pure nitrogen, while within the quartz vessel a magnesium spark gap was generated (Fig. 5). We then worked up the irradiation products so obtained in an air-sealed container, freed them of unprocessed ergosterol, and investigated their rotation, ab-

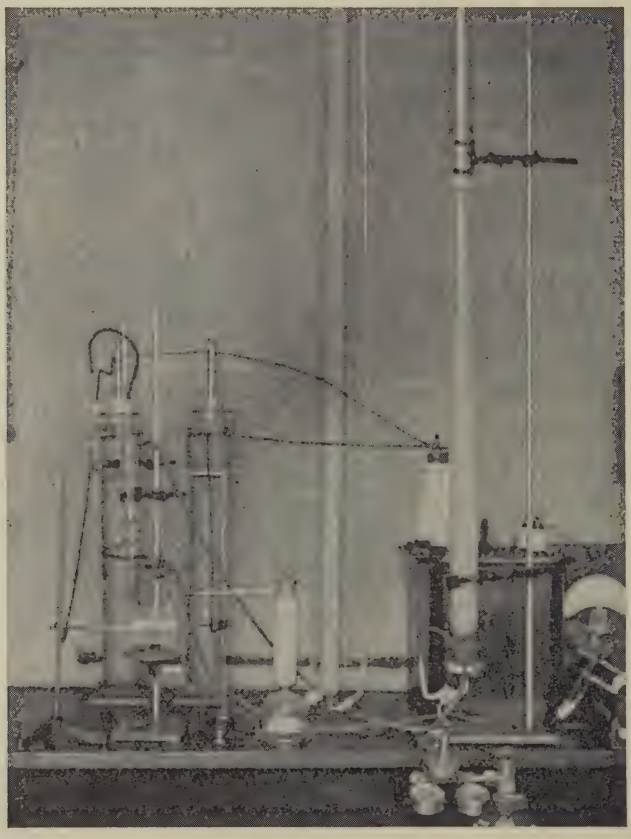


Fig. 5.

sorption spectrum, physiological effect, and analytical composition. While the physiological effect was entirely good, we made the surprising observation that our irradiation products always contained between 2% and 4% too little carbon; moreover, the numerous nitrogen-containing esters which we have examined did indeed yield a correct atomic relation between C and N, but always in too low percentages. The deficit can only be based on an absorption of oxygen by the activated ergosterol. We therefore proceeded to refine our nitrogen with even greater care, and for that purpose we made use of Kautsky's apparatus. Here we had success in so far as the deficit in carbon decreased to between 0.5% and 1.5%, depending on the period of irradiation. But even so, we never obtained entirely correct analytical composition. We first obtained incontestable values when we irradiated solutions of ergosterol in highly evacuated, sealed quartz vessels, with constant agitation. Under these conditions irradiation products arise which not only give an analytical composition exactly of the formula $C_{27}H_{42}O$, but also yield a number of crystallized derivatives of correct analytical composition.

There can, then, remain no doubt that ergosterol does not change its analytical composition under irradiation. The only remaining possibility is that ultraviolet light has either a polymerizing or an isomerizing effect upon ergosterol. In order to test experimentally the possibility of a polymerization, we undertook to ascertain the molecular weight of irradiated ergosterol, and found values which fall within the margin of error for the simple molecular weight. Thus a demonstrable polymerization does not take place during irradiation.

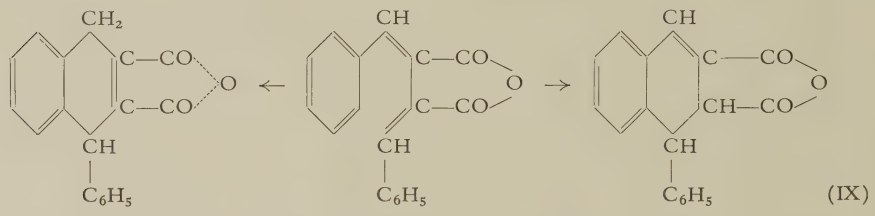
There are a number of possibilities for the process of isomerization. First, it might be assumed that a displacement of the secondary alcohol group to a double-bond took place, by which the unsaturated alcohol group (VII) would be transformed into a saturated ketone group (VIII).

(VII) (VIII)

In this process the hydroxyl group would thus disappear. We therefore tested whether the hydroxyl content of the irradiation product of ergosterol is the same as of ergosterol itself, and for this we made use of Zerewitinoff's method. Unirradiated ergosterol gave in a series of determinations a mean value of 1.02 active hydrogen atoms, irradiated ergosterol gave a mean value of 1.11 active hydrogen atoms per molecule. The determinations thus demon-

strate that the hydroxyl group does not disappear during irradiation, and that therefore the first of the possibilities under discussion for isomerization collapses. Moreover, we have prepared the isomer in question here, ergostadienone, and established that it is ineffective antirachitically.

As a second possibility for an isomerization, it must be taken into consideration that during irradiation a double bond rearranges itself as a ring bond. Stobbe discovered a similar reaction to light (see (IX)) in the phenylfulgids, which are transformed into dihydro-naphthalene derivatives.

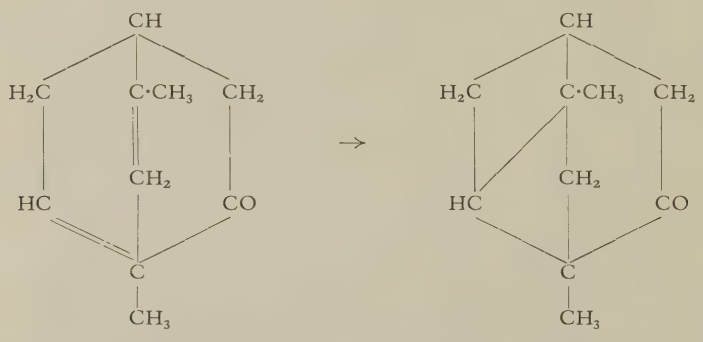


(IX)

1-Phenyl-1,4-dihydronaphthalene-2,3-dicarboxylic acid anhydride ← Diphenylfulgid → 1-Phenyl-1,2-dihydronaphthalene-2,3-dicarboxylic acid anhydride

In the photoisomerization of carvone (X) even two double bonds would disappear (XI).

In order to test whether the number of double bonds alters during the ultraviolet irradiation of ergosterol, we employed titration with perbenzoic acid and quantitative catalytic hydrogenation. The measurements gave the result that, like the hydroxyl group, the number of double bonds remains unaltered with irradiation, and even with excessive irradiation.



(X) Carvone

(XI) Carvone-camphor (?)

The isomerization therefore is based on a displacement of double bonds or a steric rearrangement here or at another position in the molecule.

The nature of these displacements or rearrangements has not yet been determined; for as yet too little is known about the more detailed structure of ergosterol. It is, however, important that also the saturated perhydration products of ergosterol, and of its irradiation product, which both have the formula $C_{27}H_{48}O$, are different.

Biography

Adolf Windaus was born in Berlin on December 25, 1876, the son of Adolf Windaus and Margarete Elster. His ancestors had for generations mostly been artisans (from his father's side, drapery manufacturers).

After attending the renowned « Französisches Gymnasium » (French grammar school) in Berlin, where his interests were mainly focussed on literature, he took up medicine in 1895 (in Freiburg i.Br. and in Berlin), passing his preliminary medical examinations (« Physikum ») in 1897.

He had been particularly fascinated by Emil Fischer's lectures during his stay in Berlin and in consequence he began studying chemistry at Freiburg i.Br. under Kiliani, at the same time continuing his medical studies. In the winter of 1899–1900 he obtained his Dr. phil. degree, the subject of his thesis dealing with the cardiac poisons of the Digitalis plant.

Windaus chose zoology as his subsidiary subject on account of the deep impression which Weismann's lectures had made on him in Freiburg. After graduating Windaus moved to Berlin to work with Emil Fischer. It was there that he met Otto Diels, with whom he formed a life-long friendship. He returned to Freiburg i.Br. in 1901 and on Kiliani's suggestion began his work on cholesterol and related sterols. Windaus's decision to study these substances was based on the fact that nothing was known about the structure of cholesterol at the time and he expected that investigations in this field would yield new and unexpected results. From the very start he correctly believed that sterols, which occur in every cell, must be considered as the parent substance of other groups of natural substances. Based on this work, briefly entitled *On Cholesterol*, Windaus « habilitated » as lecturer in 1903. In 1919 he succeeded in transforming cholesterol into cholanic acid, which had previously been isolated from the bile acids by Wieland – another close friend of his who received the Nobel Prize in 1927 for his studies of the constitution of the bile acids and related substances – Windaus thus demonstrated that the bile acids are closely related to the sterols.

Another rich field of investigation from biological viewpoint was that

of imidazole derivatives. This work, carried out in collaboration with Knoop, resulted from his attempt to prepare natural amino acids through the action of ammonia on sugar, and thus to establish conversion of sugar into proteins. The production of imidazole derivatives as a result of this reaction induced him to demonstrate the presence of a prototype of the imidazole ring in proteins. This in turn led to his demonstration that histidine, a building-stone of proteins, is an imidazole alanine, and to his discovery of histamine (imidazole-ethylalanine), a hormone of great importance in physiology and pharmacology, which was the reason for the interest shown by German chemical industry in his work.

As the foremost expert on sterols he was in 1925 invited by the American physiologist Alfred Hess to come to New York to cooperate in the study of the antirachitic vitamin.

It was also his interest in the imidazole derivatives that prompted him to examine the structure of the antineuritic vitamin. Cooperating with the I. G. Farbenindustry, which supplied the precious raw material for the work, he was able to prove that not an imidazole-ring (as suggested by Jansen and Donath), but a thiazole- and a pyrimidine-ring are present in vitamin B_1.

Other research taken up by Windaus was into the stereochemical problems of the *cis*- and *trans*-linking of hydrogenated ring systems. In all these investigations his starting-point was always that of experimental observation, and not of theoretical deduction; the inductive method was the most suitable for his talents. During the last years of his life he also investigated the possibility of chemotherapy in cancer research.

Windaus was appointed Assistant Professor (1906), and Professor of Applied Medical Chemistry at Innsbruck University (1913), where he remained for two years. He moved to Göttingen in 1915 as Professor of Chemistry, succeeding Otto Wallach, where he stayed until his retirement in 1944 as Director of the Laboratory for General Chemistry, formerly the Wöhler Institute. Among his pupils may be mentioned Adolf Butenandt, Nobel Prize winner 1939 for his work on sex hormones – which are closely related to the sterols – and Hans Brockmann.

Windaus received the Nobel Prize in Chemistry in 1928, on account of his work on the constitution of sterols and their connection with vitamins. Among the many honours he was awarded were the Pasteur Medal (1938), the Goethe Medal (1941), also the «Groszes Verdienstkreuz» (Grand Order of Merit) in 1951, and the «Groszes Verdienstkreuz mit Stern» (Grand Order of Merit with Star) in 1956. In addition he was recipient of the Order pour

le Mérite, Peace Class, in 1952. He was also honorary doctor of the Universities of Göttingen, Munich, Freiburg, and Hanover.

Professor Windaus married Elisabeth Resau in 1915. There were three children by his marriage: Günter (b. 1916), Gustav (b. 1918), and Margarete (b. 1921).

He died on June 9, 1959.

Chemistry 1929

ARTHUR HARDEN

HANS KARL AUGUST
SIMON VON EULER-CHELPIN

«for their investigations on the fermentation of sugar and fermentative enzymes»

Chemistry 1929

Presentation Speech by Professor H.G. Söderbaum, Chairman of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

The fermentation of liquids containing sugar – there we have a chemical reaction older than all chemical science. The point of time when men first began to take this reaction into their service is really lost in the mists of antiquity, before the beginning of history. The peculiar and apparently self-caused process by which an innocent fruit juice is transformed with the active formation of scum, into a drink which is either stimulating or intoxicating according to the quantity partaken, attracted attention in the very earliest times; and to many peoples it appeared so wonderful that nothing less than the cooperation of a divinity seemed to them possible as an explanation.

Our enlightened time has scarcely the right to marvel at this, when we take into consideration how long a time science has since required to obtain an acceptable conception of the nature of fermentation. Here we stand face to face with one of the most complicated and difficult problems of chemical research. Little more than a couple of centuries separate us from the time when men first began to perceive that the fermenting substance was sugar, which under the influence of a certain *something* was decomposed, with carbonic acid and ethyl alcohol as the final products of the decomposition.

But what this « something » was, and how it worked, still remained unsolved questions, long defying the most penetrating attempts at interpretation. It was not until our own days that it has been vouchsafed to us to have a fairly satisfactory answer to these questions, but even here the process of development has been slow, toilsome, and it took place, so to speak, in several instalments.

In carrying out the provisions of Alfred Nobel's Will, the Swedish Academy of Sciences has already once before had its attention directed to this sphere of research. That was in 1907, when Eduard Buchner was awarded the Nobel Prize in Chemistry for his discovery of non-cellular fermentation. At the time complaints were raised in certain quarters against this award as being insufficiently justified. Seen in the perspective of distance in time, however, Buchner's discovery has more and more stood out as a line of demarcation

between two different epochs, pointing the way to a new phase in the history of the chemistry of fermentation.

Buchner's discovery marked the final decision in a long struggle between two distinct schools – one, the older one, represented by Justus von Liebig the other, the younger one, represented by Louis Pasteur. According to the former school, fermentation was a purely chemical process, evoked by an unorganized ferment with unstable properties, which were imparted to the fermenting substance and thereby brought about its decomposition. According to the latter school, it was rather a physiological process, inseparably connected with the vital act of a microorganism known as the « fungus of fermentation ». Buchner's discovery made it evident that to some extent both were right, but also to some extent both were wrong, and, consequently, that the truth lay between the two.

But the value of the discovery makes itself known in a still more definite way through the impulse it has given to later research. In fact, during the last three decades that research has made such great advances, has given such an enlarged insight into the mechanism of the process of fermentation, that the Academy of Sciences has found the time ripe once again to award a Nobel Prize in this department. In so doing the Academy has deemed it right to divide equally the Nobel Prize in Chemistry for the present year between Professor Arthur Harden and Professor Hans von Euler.

Buchner assumed in the yeast-juice the presence of a uniform ferment or enzyme, known as « zymase ».

When, however, Harden and his fellow-workers filtered a quantity of Buchner's yeast-juice through a gelatine filter, known as an « ultrafilter », and thereby split it up into two fractions (a filtrate and a sediment that did not pass through the filter), the curious state of things occurred that neither of these fractions was any longer able to bring about fermentation, but that after being mixed with one another they recovered that capacity.

Harden explained this by saying that a high-molecular enzyme, the zymase proper, was left on the filter, which let through a low-molecular complementary enzyme, which for the sake of brevity was called co-enzyme or co-zymase.

Another no less important advance is made in Harden's demonstration of the hitherto neglected part played by phosphoric acid in the process of fermentation. It has been found that a certain addition of phosphate gives rise to an equivalent amount of carbonic acid and ethyl alcohol. This effect is asso-

ciated with the formation of one or more definite compounds between sugar and phosphoric acid – known as the « zymo-phosphates », amongst which a glucose monophosphate and a glucose diphosphate are to be regarded as the most important.

In the same measure as research in this department has made new conquests, a clearer and clearer insight has been gained into the importance of this discovery. In particular the work of von Euler and his pupils during the last few years greatly contributed to the unravelling of the mechanism of phosphorization.

The primary function of phosphoric acid in fermentation consists, according to von Euler, in the fact that in cooperation with an enzyme it gives rise to glucose monophosphate, identical with the monophosphate discovered by Harden and Robison. This phosphate afterwards undergoes a mutation in the presence of co-zymase, inasmuch as a glucose diphosphate and an active glucose are formed, after which the latter yields the necessary material for the subsequent stages of the fermentation.

This demonstration of the part of mutase played by the co-zymase, or in other words of the identity of co-zymase and co-mutase, is of fundamental importance, for it has fully revealed the central position in the process of fermentation of the complementary enzyme in question.

The researches of von Euler and his pupils have further led to the concentration of the co-zymase and to a far more exact study of its properties than had been previously possible. They have been able to determine approximately its molecular weight, which has been found to be about 490; and they have also been able to draw certain definite conclusions concerning its chemical nature, which make it highly probable that we have here what the chemists call a pentosenucleoside. The production of a co-zymase with a high activity has also shown in a brilliant manner the character of that enzyme as a specific activator.

Finally, what gives special interest to the study of the complicated reaction mechanism of the fermentation of sugar is that it has been possible to draw from it important conclusions concerning carbohydrate metabolism in general in both the vegetable and the animal organism.

The brief summary which has now been given, and which, in view of the scanty time allowed, has necessarily been extremely fragmentary, will in any case probably have shown that there is an extremely intimate connection between the researches of Harden and von Euler in this field. On the one

hand, the fundamental discoveries of Harden have formed the precondition and point of departure for the various work of von Euler; and on the other hand, it is only the work of the latter that has made fully evident the importance of Harden's discovery.

Under such circumstances the Academy of Sciences has not hesitated this time to avail itself of the expedient that is offered by the Statutes of the Nobel Foundation of dividing the prize between two equally meritorious scientists.

Professor Harden. When the Royal Swedish Academy of Sciences resolved to adjudge to you, together with Professor von Euler, this year's Nobel Prize in Chemistry on account of your important contributions to our knowledge of alcoholic fermentation, the Academy had let herself guided by a firm conviction that these contributions had opened indeed a new chapter in the investigation of that very complicated matter.

It is with the most sincere gratification that I have the honour of conveying to you the congratulations of the Academy on this distinction, the outward signs of which you are now about to receive.

Professor von Euler. It is a great pleasure to the Swedish Academy of Sciences to be able to award this time the Alfred Nobel's Prize also to one of her members, and so much more since during a long series of years we have been in the position to follow from nearby your energetic, persevering, and systematic investigations. The Academy is also firmly convinced that the distinction which has fallen upon you today, will not contain for you the temptation to rest on laurels already obtained, but that on the contrary it will mean a stimulus to continued and, as we all hope, successful work in the service of biochemistry.

Arthur Harden

The function of phosphate in alcoholic fermentation

Nobel Lecture, December 12, 1929

The discovery that phosphates play an essential part in alcoholic fermentation arose of an attempt by the late Dr. Allan Macfadyen to prepare an anti-zymase by injecting Buchner's yeast-juice into animals. As a necessary preliminary to the study of the effect of the serum of these injected animals on fermentation by yeast-juice, the action of normal serum was examined. It was thus found that this exerted a two-fold effect: in its presence the action of the proteolytic enzymes of the yeast-juice was greatly diminished, and at the same time both the rate of fermentation and the total fermentation produced were considerably increased. In the course of experiments made to investigate this phenomenon, which it was thought might have been due to the protection of the enzyme of alcoholic fermentation from proteolysis by means of an anti-protease present in the serum, the effect of boiled autolysed yeast-juice was tested, it being thought that the presence of the products of proteolysis might also exert an anti-proteolytic effect. As my colleague Mr. Young, who had by this time joined me, and myself had fortunately decided to abandon the gravimetric method chiefly used by Buchner in favour of a volumetric method which permitted almost continuous observations, we were at once struck by the fact that a great but temporary acceleration of the rate of fermentation and an increase in the CO_2 evolved proportional to the volume of boiled juice added were produced. This was ultimately traced to the presence of two independent factors in the boiled yeast-juice, a thermostable dialysable co-enzyme now often known at the suggestion of von Euler as co-zymase, and inorganic phosphate.

With regard to the phosphate subsequent experiments showed that in all fermentations brought about by preparations obtained from yeast the presence of phosphate is absolutely essential. Leaving aside the question of living yeast for consideration later on, three different types of fermentation can be established (See Curves 1, 2, and 3, in Fig. 1) with such preparations.

1. A relatively rapid fermentation (Curve 1, Fig. 1) in which sugar is decomposed into CO_2 and alcohol, and simultaneously inorganic phosphate is converted into an ester (or esters) of a sugar which accumulates. When the

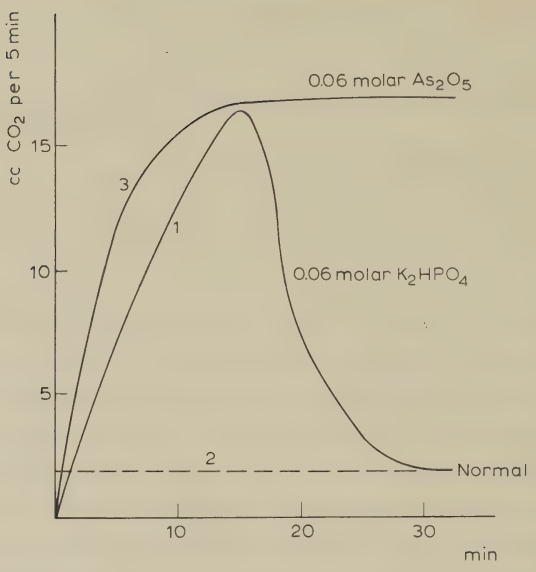


Fig. 1. Fermentation of yeast-juice.

supply of inorganic phosphate ceases, the rate of fermentation falls, the accumulation of ester also naturally ceases, and the fermentation passes into Type 2.

2. A relatively slow fermentation (Curve 2, Fig. 2) in which the rate at which fermentation occurs is controlled by the rate at which inorganic phosphate is supplied by the hydrolysis of the phosphoric esters present in the system by the phosphatase also present. This inorganic phosphate is alternately reconverted into a sugar-phosphoric ester and again liberated by hydrolysis, and thus fermentation proceeds at a steady rate in the presence of available sugar without any permanent increase in the amount of inorganic phosphate or of phosphoric ester present. This is the type of fermentation which goes on when sugar is added to an active preparation from yeast and the process is allowed to proceed until a steady rate is obtained. In some preparations, depending on the amount of phosphatase present, the rate of fermentation is increased to some extent if more of the sugar-phosphoric ester is added or produced (See E. Boyland, *Biochem. J.*, 23 (1929) 219), but this soon reaches a limit. If inorganic phosphate be added, the fermentation passes into Type 1.

If sugar fails, inorganic phosphate appears and ultimately (unter favourable conditions) the whole of the sugar-phosphoric ester is hydrolysed, its sugar moiety fermented and the whole of the phosphate liberated in the inorganic form.

3. If now into a fermentation mixture in which a Type 2 fermentation is

proceeding an additional quantity be introduced of a phosphatase, capable of hydrolysing the sugar-phosphoric ester and thus increasing the rate of supply of inorganic phosphate (Harden and Macfarlane, unpublished results), the rate of fermentation also rises. If a sufficiently active preparation of phosphatase could be added, so that the sugar-phosphoric ester was decomposed as rapidly as it was formed, a rapid fermentation would ensue, unaccompanied by accumulation of phosphoric ester. This has not yet been accomplished directly, but an indirect method of attaining the same end is available, inasmuch as arsenates have been found to have the power of greatly stimulating the effect of the phosphatase. This observation was in reality the undeserved reward for thinking chemically about a biochemical problem. In many chemical reactions the type of compound concerned is the main fact of importance, arsenates react like phosphates, potassium may be replaced by sodium, iron by nickel or cobalt. Biochemically the difference between potassium and sodium may be the difference between life and death, and when iron is not used in a respiratory pigment it is not replaced in nature by nickel or cobalt, but by copper or vanadium. So, also, arsenate does not play a similar part to phosphate in fermentation, but acts in an entirely different manner. On the addition of a suitable amount of arsenate, a rapid fermentation (Curve 3, Fig. 1) occurs comparable in rate with that of Type 1, but differing from this in that the rate is permanently raised and that no accumulation of the sugar-phosphoric ester occurs. Under optimal conditions the addition of inorganic phosphate does not produce any significant rise in the rate of fermentation, as the rate of fermentation is controlled under these circumstances by the concentration of the fermenting complex (enzymes + co-enzyme). Arsenate on the other hand does not increase the maximum rate in fermentations of Type 1, as the supply of inorganic phosphate is already optimal.

Without making any assumption as to the exact nature of the phosphoric ester actually produced, the changes so far considered may be illustrated by the two equations, originally proposed by Harden and Young for the case in which only hexose diphosphate is formed, the first representing the evolution of CO_2 and production of alcohol, accompanied by the accumulation of ester, and the second the hydrolysis of this ester with liberation of a hexose and mineral phosphate.

$$2C_6H_{12}O_6 + 2Na_2HPO_4 \rightarrow C_6H_{10}O_4(PO_4Na_2)_2 + 2H_2O + 2CO_2 + \\ + 2C_2H_6O \quad (1)$$

$$C_6H_{10}O_4(PO_4Na_2)_2 + 2H_2O \rightarrow C_6H_{12}O_6 + 2Na_2HPO_4 \quad (2)$$

Eq. (1) represents the controlling reaction in a fermentation of Type 1, Eq. (2) that in a fermentation of Type 2. In the presence of arsenate the hydrolysis of hexose phosphate according to Eq. (2) proceeds sufficiently rapidly to supply phosphate at such a rate that Eq. (1) proceeds at maximum velocity.

Fermentation by living yeast

A striking feature of fermentation by yeast preparations is that it proceeds much less rapidly than fermentation by a corresponding amount of living yeast. Thus Buchner's yeast-juice ferments at only about $^1/_{20}$–$^1/_{40}$ of the rate of the yeast from which it is derived.

The fact that the rate of fermentation of such a juice can be raised under favourable circumstances some 10–20 times simply by increasing the supply of phosphate seems to me to indicate clearly that a large fraction, at least half, of the fermenting complex of the yeast has escaped injury in the preparation and has passed into the juice, but that the mechanism for the supply of inorganic phosphate has been to a large extent destroyed. Neither arsenate nor phosphate has an accelerating action on the rate of fermentation by living yeast. This may be due to the fact that the supply of inorganic phosphate in the interior of the yeast-cell is already optimal, but some doubt exists as to whether or not these salts freely penetrate the cell. If, however, as seems to me probable, it is true that in the preparation of yeast-juice, etc. it is the phosphate-supplying mechanism that is thrown out of gear, it becomes an object of enquiry in what way this is brought about.

Several possibilities present themselves. As suggested for the fermenting complex itself by von Euler and his colleagues, the phosphatase may in large part be combined with the cytoplasm and thrown out of action when the cell is killed. Another possibility is that in the cell the action is localized and that disorganization of the cell leads to less favourable conditions (e.g. concentration, presence of inhibitors, etc.) and to lessened rate of action. There is some evidence for this since the amount of phosphatase present, as judged by the normal rate of fermentation (Type 2), seems to diminish as the disorganization of the cell becomes more complete. Thus dried yeast and yeast dehydrated with acetone ferment sugar (Type 2) more rapidly than yeast-juice, although when phosphate is freely supplied they all cause fermentation at about the same rate. Again some labile substance which acts as an accelerator of the phosphatase may be inactivated by the various modes of treatment (grinding,

drying, treatment with toluene or acetone, etc.) to which the cell is subjected.

The process least likely to inactivate an accelerating substance is probably that used by Buchner, but the possibility also exists that such a substance, if present, might be adsorbed and thus removed from the juice by the large quantity of kieselguhr employed.

Experiments (not yet published) have recently been made in my laboratory by Miss Macfarlane to find out at what stage in the process the change occurs and whether a juice richer in phosphatase could be obtained by modifying the process of grinding and pressing out. It appears, however, that simple grinding with sand produces a change of the same order as that observed in Buchner's yeast-juice. The experiments were made by grinding a mixture of sand and yeast for different times and testing the rate of fermentation and response to phosphate at intervals of the whole mass without pressing out (Fig. 2).

These curves show the rate of fermentation of 2 g of yeast + 2 g of sand in 20 c.c. of 10% fructose at 30°: (*a*) without grinding, (*b*) after grinding for 20 minutes, and (*c*) after grinding for 60 minutes. At the point marked with an arrow 0.6 c.c. of 2 *M* K_2HPO_4 was added.

The curves show that the longer the period of grinding, the lower the rate of fermentation and the greater the response to phosphate. Here again the total loss of fermenting power was only small.

Minor differences were observed when different substances were substi-

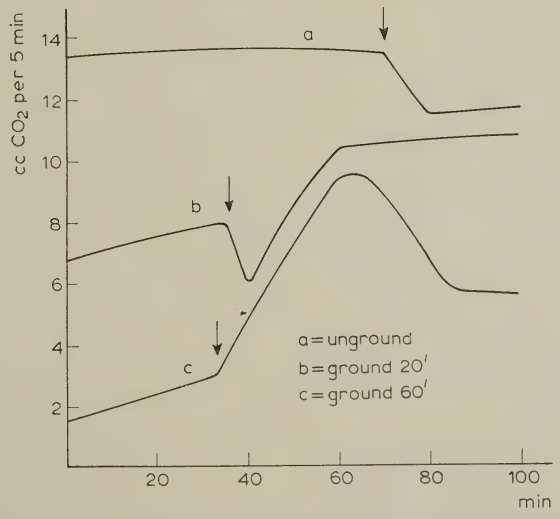


Fig. 2. Fermentation of yeast sand mixture. (At ↓ an addition of phosphate was made.)

tuted for the kieselguhr used by Buchner, the most active juice for example being obtained by the use of $CaCO_3$ whereas $BaCO_3$ yielded totally inactive material.

Further investigation may possibly throw more light on this aspect of the question.

I have spoken hitherto on the assumption that the processes in the living cell are essentially of the same kind as those which occur in the various preparations made from the dead cell, but differ from these mainly in the relative intensity of some of the reactions, and I know no valid argument against this assumption.

The cycle undergone by the phosphate in the series of changes which constitutes ordinary fermentation clearly consists in the alternate formation of a phosphoric ester and the hydrolysis of this to free phosphoric acid. A simple calculation based on the phosphorus content of living yeast shows that the whole of this phosphate must pass through the stage of phosphoric ester every five or six minutes in order to maintain the normal rate of fermentation, whereas in an average sample of yeast-juice the cycle, calculated in the same way, would last nearly two hours.

Nature and function of the phosphoric esters produced

If we next consider the exact nature of these phosphoric esters and the relation of their formation and hydrolysis to the decomposition of the sugar molecule, we are met with a singularly complex condition of affairs, which cannot yet be interpreted satisfactorily.

The main facts seem to be as follows.

When fermentation of sugar by yeast preparations is carried out under suitable conditions in presence of added inorganic phosphate, a rapid production of CO_2 and alcohol occurs and a phosphoric ester of a sugar accumulates, the amount of phosphate found in this form being approximately proportional in the ratio (CO_2/PO_4) to the increased production of CO_2 and alcohol caused by the addition of the phosphate (Kluyver and Struyk, it is true, have found lower ratios than this, but there is no doubt that high ratios 0.8–1 are often observed).

The phosphoric ester produced, however, may consist mainly of the hexose diphosphate originally described by Young and myself or of the hexose monophosphate described by Robison and myself and subsequently studied by

Robison or it may be a mixture of these in any proportions. In the case of fermentation by dried yeast (and possibly of other preparations) a further complication is afforded by the fact that a disaccharide-phosphoric ester (trehalose monophosphate) may also be present.

This conclusion is founded in the first place on a large amount of experience which has been gained at the Lister Institute in preparing hexose mono- and diphosphate. These preparations are as a rule carried out by making repeated additions of phosphate and sugar to a fermenting mixture of yeast-juice or dried yeast and fructose (or glucose). With dried yeast a large proportion of the diphosphate is usually obtained, and the relatively small amount of monophosphate produced contains a considerable proportion of trehalose monophosphate. With yeast-juice the results are very variable and no trehalose monophosphate has so far been detected among the products. More precise experiments have been made by Lord Henley and myself in which the gas evolved after a single addition of phosphate was carefully measured and the proportions in which mono- and diphosphates were produced were determined as accurately as possible. Unfortunately, the available methods are not very good, as they rest on the solubilities of the different compounds in 10% alcohol, and these are to some extent mutually affected in the presence of both compounds. Further, yeast, like Africa, is always yielding something new, and the recently discovered fact that pyrophosphates exist in yeast and by their formation from, or hydrolysis to, orthophosphates may cause disappearance or appearance of «inorganic phosphate» adds another source of inaccuracy to the many previously known.

Allowance has, of course, to be made for the phosphorus compounds existing in the mixture at the moment of addition of inorganic phosphate and for the normal evolution of CO_2 which occurs throughout the experimental period in addition to the enhanced evolution due to the esterification.

In spite of these minor uncertainties the somewhat surprising fact emerges, that whatever the nature of the phosphoric ester which accumulates, the CO_2 is approximately equivalent in the ratio $CO_2 : PO_4$ to the amount of phosphate which undergoes esterification. The full results are given in two papers published recently by Lord Henley and myself in *The Biochemical Journal* and need not be quoted in detail here. The experiments indicate the wide variation which may occur in the nature of the hexose phosphate produced whilst the ratio of $CO_2 : PO_4$ esterified remains constant and approximately equal to unity. Two extreme cases may be quoted, in one of which 13.5% of the PO_4 esterified was present as hexose diphosphate and 86.5% as monophosphate

and in the other 97% as diphosphate and only 3% as monophosphate; the CO_2/PO_4-esterified ratios were 0.98 and 0.86 respectively.

I do not propose to discuss in any great detail the various theories which have been proposed to explain these complicated relationships. It would be natural to assume that the introduction of the phosphoric acid group into the sugar molecule, forming a hexose monophosphate, might render this more accessible to decomposition into the compound (or compounds) containing three carbon atoms which are now accepted as an intermediate stage in the production of CO_2 and alcohol. The phosphate radical from one of these groups might then serve to convert another molecule of the monophosphate into the stable diphosphate (Meyerhof) $2C_6H_{11}O_5PO_4H_2 \rightarrow C_6H_{10}O_4(PO_4H_2)_2 + 2CO_2 + 2C_2H_6O$, or two of the three carbon groups containing each one phosphate group might unite with each other, forming the stable diphosphate (Kluyver and Struyk) $2C_6H_{11}O_5(PO_4H_2) \rightarrow 2C_3H_6O_3 + 2C_3H_5O_2(PO_4H_2) \rightarrow 2CO_2 + 2C_2H_6O + C_6H_{10}O_4(PO_4H_2)_2$. Any monophosphate escaping these reactions would be found as a constituent of the mixed hexose phosphates resulting from the fermentation.

To add further to the difficulty of unravelling this complex tangle it must be remembered that, whether glucose or fructose be fermented, the hexose diphosphate produced is probably a derivative of fructose, or at least yields fructose on hydrolysis, whilst the monophosphate is with equal probability a mixture of about 80% of a glucose monophosphate and 20% of a fructose monophosphate. It is obvious from this that whatever changes occur are not limited to the simple introduction or removal of a phosphoric acid group, fundamental changes occur in the constitution of the molecule of the sugar itself.

Attractive as is the theory of the intermediate character of some one of the hexose phosphates, it seems to me impossible at the moment to bring it into agreement with some of the facts which have just been related. The production of 70–80% of the monophosphate, with an unaltered degree of formation of alcohol and CO_2, renders it impossible that this ester should be « obviously nothing but a part of the intermediate product which has escaped the coupled decomposition–esterification reaction » (O. Meyerhof and K. Lohmann, *Biochem. Z.*, 185 (1927) 155).

It appears to me that the fundamental idea expressed in the original equation of Harden and Young is nearer the truth than any alternative that has as yet been suggested. A coupled reaction of some kind occurs, as the result of which the introduction of two phosphate groups into certain sugar molecules – either into the same molecule or one each into two different ones – induces the de-

composition of another molecule. The introduction of these phosphate groups in presence of muscle extract and presumably in both muscle itself and yeast, is actually accompanied by a small evolution of heat (O. Meyerhof and J. Suranyi, *Biochem. Z.*, 191 (1927) 106), and it is possible that this may have some significance for the occurrence of the coupled reaction. What are the conditions for the preferential formation of the mono- or di-ester we do not yet certainly know, although the work of Kluyver and Struyk suggests that dilution of the enzyme may be one factor in this.

The lack of exact chemical equivalence among the products (ester on the one hand, CO_2 and alcohol on the other) is probably more easily explicable on this view than on any other.

The mechanism of the fermentation of the monoester has not yet been worked out in sufficient detail to afford valid evidence either for or against the theory, but Dr. Robison and I have made experiments (about to be published) which show that the monophosphate itself reacts with a further quantity of phosphate and that this reaction is accompanied by an enhanced production of carbon dioxide and alcohol.

Sugar metabolism in vegetable and animal organisms

After the establishment of the important part played by phosphates and phosphoric esters in alcoholic fermentation, it was soon found by various workers that these compounds provided the clue to many other biological phenomena. The co-zymase of alcoholic fermentation was found by Meyerhof to exert an equally important part in the respiration of yeast, and the important observation was made also by Meyerhof that it occurred in muscle and was an essential factor in the carbohydrate metabolism of muscle, in which the intervention of a hexose phosphate had been proved by Embden. This phenomenon was shown to take place on lines quite similar to those of the respiration and fermentation of yeast, and in 1924, before the riddle of lactic acid formation had been completely solved, O. Meyerhof wrote (*Chemical Dynamics of Life Phenomena*, 1924): « It may indeed be considered a success of general physiology and its mode of experimenting, that the chemical dynamics of a highly differentiated organ like the muscle could be partly revealed by the study of alcoholic fermentation of yeast. » But a still greater success was to follow. An astonishing degree of similarity was shown to exist between almost every detail of the production of lactic acid by the muscle enzymes and of

alcohol by the yeast enzyme, which extended to the identity of the phosphoric esters concerned, the accumulation of ester under similar conditions, and even to the effect of arsenate on the process. After the publication of Meyerhof's preliminary papers in which these observations were recorded I wrote the following passage in concluding a short review of the work (*Nature*, 118 (1926) Dec. 18th) which I may perhaps be allowed to quote: « The striking similarity established by Meyerhof between the changes of carbohydrates in muscle and in the yeast cell is seen to be much closer than has been believed. The remarkable phenomena accompanying alcoholic fermentation are now duplicated in the case of lactic acid production, and it may reasonably be expected that most of the fermentative decompositions of the sugars will be found to be initiated in a similar manner. »

Direct proof is still wanting in many cases, but some instances are known among bacteria (Virtanen), moulds (von Euler and Kullberg) and higher plants (Ivanoff, Bodnar). It is not too much to say that the fundamental biological mode of attack on carbohydrates is that revealed by the study of alcoholic fermentation.

Ossification

Another biochemical function of the hexose phosphates which is shared by other hydrolysable phosphoric esters is that of being a potential source of phosphate ions. I am happy to say that one of the most beautiful and important developments of this idea has been worked out quite independently at the Lister Institute by Dr. R. Robison as a direct consequence of his work on the hexose monophosphate of yeast-juice.

« During my investigation of the hexose monophosphoric acid isolated from the products of fermentation », he says (*Biochem. J.*, 17 (1923) 286) « the hydrolysis of the ester by enzymes was studied. In some experiments in which the readily soluble calcium and barium salts were used as substrates, the progress of the hydrolysis was shown by the formation of a precipitate of sparingly soluble calcium or barium phosphate

$$C_6H_{11}O_5PO_4Ca + H_2O \rightarrow C_6H_{12}O_6 + CaHPO_4$$

The formation of this precipitate suggested to me the query whether some such reaction might conceivably be concerned in the deposition of calcium phosphate during the formation of bone in the animal body. In the first place I

sought for an enzyme capable of effecting hydrolysis in the bones of growing animals. »

The search was successful, a « bone phosphatase » was found in the ossifying cartilage of young animals and a series of interesting and important investigations has followed, as a result of which I have little doubt that their author is on the highway to the chemical explanation of the process of ossification – a good instance of the far-reaching and unexpected results flowing from observations made for quite a different purpose.

Biography

Arthur Harden was born in Manchester, England, on October 12, 1865; his father was Albert Tyas Harden and his mother Eliza Macalister. He was educated at a private school in Victoria Park (1873–1877) and at Tettenhall College, Staffordshire (1877–1881). He entered The Owens College in the University of Manchester in 1882, studying under Sir H. E. Roscoe, and graduated in 1885 with first-class honours in chemistry. In 1886 he was awarded the Dalton Scholarship in Chemistry and he spent twelve months during 1887–1888 working with Otto Fischer at Erlangen. He returned to Manchester as lecturer and demonstrator, and remained until 1897 when he was appointed chemist to the newly founded British Institute of Preventive Medicine, which later became the Lister Institute. In 1907 he was appointed Head of the Biochemical Department, a position which he held until his retirement in 1930, and in 1912 he received the title of Emeritus Professor of Chemistry, University of London. He continued his scientific work at the Institute after his retirement.

Before he went to London, Harden had studied the action of light on mixtures of carbon dioxide and chlorine. He entered the Institute with an excellent chemical background and applied his methods to the investigation of biological phenomena (among others: the chemical action of bacteria and alcoholic fermentation). He studied the breakdown products of glucose but he was soon to be drawn to the problem of the chemistry of the yeast cell. His classic study of the chemistry of the fermentation of sugar by yeast juice, which have advanced the knowledge of the processes of intermediary metabolism in all living forms, lasted for many years and provided a stepping-stone for many research workers in allied fields. Harden himself contributed to the vitamin field with a series of papers on the antiscorbutic and antineuritic vitamins and their occurrence in food and drinks.

Harden was Joint Editor (with W. M. Bayliss) of *The Biochemical Journal* from 1913 to 1938, and, in addition wrote numerous papers in scientific journals. He is the author of *Alcoholic Fermentation*, *A New View of the Origin of Dalton's Atomic Theory*, and *Chemistry for Advanced Studies* (with Sir H. E.

Roscoe), *Inorganic Chemistry for Advanced Students*, and *An Elementary Course of Practical Organic Chemistry* (with F. C. Garrett).

Harden was knighted in 1926. He was honorary Doctor of Science, University of Athens and honorary Doctor of Laws, Universities of Manchester and Liverpool. A Fellow of the Royal Society (1909), he received the Davy Medal in 1935.

He married Georgina Sydney Bridge, daughter of C. Wynyard Bridge of Christchurch, New Zealand, in 1900. They had no children. His wife died in January, 1928, and Sir Arthur on June 17, 1940, at his home in Bourne End, Buckinghamshire.

Hans von Euler

Fermentation of sugars and fermentative enzymes

Nobel Lecture, May 23, 1930

It is my object to give a report of my work in connection with *The Fermentation of Sugars and the Enzymes Active in Such Fermentation*. In performing this duty and expressing my sincere and warm thanks to my colleagues for their very valuable assistance, I will try to give an idea of the aims of our work, point out the details of our methods and the results obtained, and clarify their relationship to central problems in biology and to what extent our work can contribute to a solution thereof.

Any scientific problem must be attacked by research into detail; the natural scientist did not win his victories until he left meditation on the great riddles of the world and began a careful study of special problems; our knowledge of more general associations and of far-reaching laws has grown out of the results of such research. Thus the study of alcoholic fermentation led men like Lavoisier, Pasteur and Liebig beyond the immediate results to experience of the greatest scope.

The fermentation of sugars forms a special reaction complex and each of the reactions co-operating therein constitutes a still more limited field of study, but it is precisely this combination of reaction phases within the cell that is in many respects typical of the processes of life.

We also know that the decomposition of sugar during fermentation is identical with the reactions by which sugar begins to burn during respiration, and there is therefore no organism whose life is not dependent on the sugar reactions under discussion.

What I shall deal with mainly in this lecture relates to the *means* by which the living cell decomposes its sugar and thus produces energy for its life and growth. By these means the reactions of the *living cell* differ from *other* chemical processes.

Within the living organism, the majority of reactions are brought about by special substances already active in minimum quantities, such substances being known as *enzymes* or ferments. Every group of substances, and in fact practically every substance, requires its specific enzyme for its reaction. Only a few enzyme types were known in the early days, such as pepsin in the gastric

juice, which splits proteins, or amylase in saliva and in malt, which converts starch into sugar, but in more recent times the number of enzymes whose existence has been proved or substantiated has risen to over 100.

A study of the kinetics of the enzyme reactions confirmed Berzelius' brilliant intuition to the effect that in respect of their activity the enzymes are analogous with the other, non-enzymatic catalysts. For example, we can split sucrose into glucose and fructose either by means of a strong acid, such as sulphuric acid, or by an enzyme obtained from yeast, namely saccharase. The difference is principally that we require much fewer molecules of enzyme (about 1 millionth) than molecules of sulphuric acid to achieve the same effect, and this is due to the fact that sucrose has a much greater affinity for the enzyme than for sulphuric acid; thus it binds its special enzyme more completely than the acid and holds it within the reaction sphere.

All earlier hypotheses to the effect that the enzymatic activity was associated with a special state of matter have been refuted; enzymes are fundamentally not different from other substances.

Enzyme research is now advancing in two complementary directions: *a purely chemical and a biological.*

With regard to the former, the problem is to unravel the *chemical nature* of the enzymes; we cannot reach any definitive conclusions if we do not know the atom combinations governing the properties of enzymes. The problem in this case therefore is to concentrate these substances, which are enormously diluted in animals and plants, then eliminate the accompanying substances from their solutions, obtain them in the pure state, and finally analyse them and unravel their molecular structure.

At the beginning of this century the work on enzymes had still been predominantly qualitative; it has become necessary for us to introduce exactly defined and rational units for the activity of enzymes if we are to be able to follow the course of purification.

Concentration and purification, which have frequently resulted in isolation of the required substance in biochemistry, come up against particular difficulties as far as enzymes are concerned. Enzyme molecules are large, unstable and are easily destroyed by acids and alkalies; with regard to their sensitivity to elevated temperature, they behave like proteins and are rapidly denatured or inactivated at temperatures above 60°. Thus it is not possible to use sharp chemical agents for their study.

Substances of high activity are obtained under mild conditions, by precipitation with alcohol and acetone, by diffusion and by adsorption methods – the

latter specially devised by Willstätter – and the unremitting work done in this respect both here and by other schools has certainly not been in vain. This preparative method, however, has hitherto had only limited success.

It was obvious to try to break through by *indirect* methods. I shall discuss these briefly for they constituted a quite important part of our research, and I also think that their continued use will give valuable results.

As I have already stated, an enzyme is active according to its combination with its substrate by a particular affinity. This combination is produced by certain atom groups, and *inter alia* it is these which have to be clarified.

I will take an example: when proteins are digested, the long chain of amino acids of which the protein consists becomes smaller and smaller, and the final intermediate product containing two such amino acids is known as a dipeptide.

The dipeptides also have their special enzymes, the *dipeptidases*. Like all such substrates, the dipeptides are bound to the enzyme before the latter acts, and the first question is *by what group in the dipeptide* does this take place. It is a general fact that the *decomposition products* arising in an enzyme reaction have an inhibiting effect, and the amino acids are the inhibitors here. We have to ascertain *which group* such a decomposition product must contain to inhibit the reaction, and by Josephson's work concerning a special dipeptidase it could be shown that it is the *amino* group that is involved here.

The study of the circumstances in which this inhibition occurs and in which the enzyme binds the dipeptide has subsequently shown that it is probably a *carbonyl* group in the enzyme that binds the substrate; and thus for the first time a combination between an enzyme and a substrate was traced back to certain atom groups.[1]

Other researchers, particularly Waldschmidt-Leitz and Grassmann, continued with this method of determining active atom groups in an enzyme molecule, firstly for the examination of peptidases from yeast and subsequently for the examination of other protein-splitting enzymes. Two defined enzyme types were discovered, *amino*-peptidases and *carboxyl*-peptidases, and confirmation was obtained for a working hypothesis devised by us, the so-called *2-affinity theory*. This means that two different reaction centres cooperate in the splitting of the substrate, namely one which binds the substrate with a measurable specific affinity and one of a shorter life which should be localized at that zone of the substrate where the splitting takes place.

Another way adopted by us to discover something of the chemical nature of the enzyme is as follows:

It was known that certain chemical substances even in very small doses are able to inactivate dissolved enzymes. Phenols, amines, mercury salts and hydrocyanic acid are among them, i.e., substances which even the layman knows as poisons. Their fatal effect on the organism consists precisely in that they inactivate the enzymes necessary to life. Systematic examination has shown that such poisoning of isolated enzymes is of *a purely chemical nature*, i.e., the poison binds the enzyme, which is thus inactivated. By studying this effect quantitatively, we determined enzyme equivalents by known quantities of poison.

Such poisoning can readily be shown with various yeast enzymes; I will take catalase and poison it with hydrocyanic acid (experiment).

The poisoning of the typical complex of alcoholic fermentation with fluoride can be proved and at the same time the co-operation of this enzyme with the activator cozymase can be proved by another experiment: the reaction can be followed in the apparatus in which we conventionally determine the course of fermentation (Myrbäck's microfermentation apparatus). *Demonstration experiment*: three pairs of flasks are filled as follows.

1 and 2 with the enzyme (apozymase) without cozymase,
3 and 4 with the enzyme with cozymase,
5 and 6 with apozymase, cozymase, and fluoride.

The experiment showed evolution of CO_2 only in flasks 3 and 4, namely 5 c.c. per 10 minutes.

The case best examined is the poisoning of the yeast enzyme which splits sucrose into its components, glucose and fructose. The degree of poisoning depends enormously on the acidity of the solution. Myrbäck's test showed that the saccharase is inactivated by silver salts to the same degree as the enzyme reacts with the *free silver base* formed from the silver salt, to form a silver compound, and similar poisoning occurs with certain other toxic metal salts, Hg, Cu, and Pb.

From the quantity of metal salt added and from the degree of poisoning, i.e., the degree to which the enzyme has been inactivated, it is possible, on certain assumptions, to determine how many mg of enzyme correspond to 1 mg of silver. Other measurements by Myrbäck have shown that the poisoning due to phosphotungstic acid, picric acid, etc., depends among other things on the formation of slightly dissociated salts between these acids and a slightly basic group in the enzyme molecule. Other series of tests have given

information concerning which important constituents within the saccharase molecule co-determine the affinity of the enzyme for its substrate.

Thus for each enzyme of the saccharase type it is possible to determine an equivalent corresponding to each poisonous metal atom. Somewhat complicated calculations are required to arrive at the said final results from the experimentally determined degrees of poisoning. Without going into these, I will simply state that on this basis we now understand how quantities of one millionth of a gram and less of a poison may be sufficient to paralyse or annihilate an organism; the quantity of the catalysts required to be inactivated in the poisoning of an organ is not greater than the quantity of poison used. There is therefore nothing mystical in the homeopathic doses.

Poisons have also been used in other ways in work on enzymes. As I stated, fermentation from sugar to alcohol and carbon dioxide passes through a considerable number of intermediate stages, amongst which each has its own enzyme. These partial reactions are so interwoven that it is difficult to separate them directly. It has now proved possible to poison the long series of reactions *partially*, so as to separate one or other partial reaction so as to cleanse the others as it were. Something along these lines has been possible with fermentations by the addition of *fluoride*. To clarify this I must give a brief idea of the view previously held concerning the various phases of fermentation.

I must first recall A. Harden's important result, namely that fermentation not only requires a catalyst of enzyme nature but also a more stable substance which was called *cozymase*.

Examination by Myrbäck in 1924 had the result that the fermentation reaction phase requiring the cooperation of the cozymase is a very early one, namely one preceding the combination with phosphoric acid.

According to Harden, the splitting of sugar is associated as follows with the formation of a phosphoric acid ester, known as phosphorylation:

$$\text{I.}\quad 2C_6H_{12}O_6 + 2PO_4HR_2 = 2CO_2 + 2C_2H_5OH + 2H_2O + \\ + C_6H_{10}O_4(PO_4R_2)_2$$

$$\text{II.}\quad C_6H_{10}O_4(PO_4R_2)_2 + 2H_2O = C_6H_{12}O_6 + 2PO_4HR_2$$

Thus a compound, *zymo-diphosphate*, is formed simultaneously with alcohol and carbon dioxide.

After the sugar has undergone conversion by its reaction with phosphate, the actual splitting takes place. The chain of 6 carbon atoms is split in the middle and amongst the possible splitting products, dioxyacetone, glyceraldehyde and methyl glyoxal it is precisely *methylglyoxal* which really does

occur according to C. Neuberg. Fermentation and respiration differ only after this stage. In the case of the former, a number of oxidation-reductions result in alcohol and CO_2, while in the case of respiration the atmospheric oxygen oxidizes that part of the resultant intermediate products which is not involved in the synthesis, to form CO_2.

I will leave the later fermentation stages and intermediate products, amongst which is pyruvic acid, and I will turn to the processes which occur when the sugar supplied to the yeast cell or the blood is involved in metabolism.

In unravelling these very complicated affairs, the thermostable activator *cozymase*, to which I shall shortly return, has given valuable guidance. The three main forms of biological sugar decomposition, fermentation, respiration and glycolysis, have a common partial reaction of the oxidation-reduction type, and a co-enzyme is active in this.

The character of this reaction is illustrated by the fact that the Cannizzaro reaction of acetaldehyde in liver is dependent on *the same co-enzyme*; this co-enzyme has also proved to be *identical with cozymase*.

This fact led to the conclusion that an oxidation-reduction, or a mutation, combined with energy equalization, is *the fermentation phase requiring the presence of the cozymase*.

In recent years this fact has been valuably supplemented by the very thorough research by R. Nilsson. According to Nilsson's result, *that part of the fermentation reaction in which the cozymase co-operates is inactivated by fluoride*. A hexose monophosphoric acid, known as the *Robison* ester, is formed as an intermediate product in this.

From the enzymatic aspect it was important that a phosphorylation could be demonstrated in these circumstances both in yeast and in muscle *without the co-operation* of cozymase and without the simultaneous evolution of CO_2. This proved the existence of an *independent phosphorylating enzyme* (H. von Euler, H. Ohlsén and S. Kullberg, 1911), a phosphatase.

Another important finding was that fluoride prevents the reaction: hexose monophosphoric acid → hexose diphosphoric acid.

Finally, I should mention the result that glucose in its isolated and stable form behaves in all biological decompositions differently from the form in which this hexose immediately arises out of the higher carbohydrates, glycogen and starch, by means of which animal and plant organisms store their sugar reserves; in other words: the form of sugar which is formed enzymatically from glycogen and from zymophosphates, behaves as *blood sugar*.

Time does not allow me here to go into the medically interesting question

of the effect of insulin on the blood sugar balance and the enzymatic changes occurring in diabetes mellitus.

Returning to my main subject, I will go back to the previously mentioned Harden equations. This formulation, which has played such a great part in modern fermentation chemistry, says nothing about the type of the assumed association between the two reactions. By a modification of Harden's formulae (H. von Euler and K. Myrbäck, 1924), the connection between the two reaction stages becomes clear.

Our first formulation was that *one* molecule of zymohexose undergoes the reaction:

$$C_6H_{12}O_6 + PO_4HR_2 = C_3H_6O_3 + C_3H_5O_2(PO_4R_2) + H_2O$$
$$2C_3H_5O_2(PO_4R_2) = C_6H_{10}O_4(PO_4R_2)_2$$

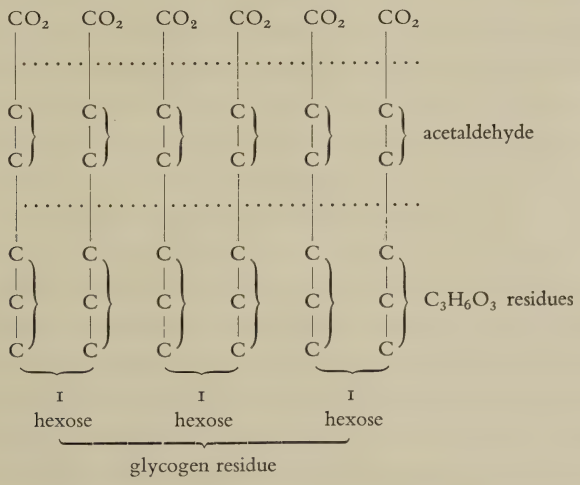
This formulation shows that the molecule which undergoes fermentation is split into two partial molecules each having three C atoms, *one of which is richer in energy and the other poorer in energy than half the substrate*, and that the zymophosphate synthesis is obtained at the expense of the fermenting hexose half which is poorer in energy. It is of course a further improvement to adopt Meyerhof's assumption of monophosphate instead of glucose as starting-material (cf. H. von Euler and K. Myrbäck, 1929[2]). The main thing, however, is the principle that phosphorylation introduces an energy dismutation within the hexose residue.

I mention this contribution because it touches on a general and biologically not unimportant question: it has long been clear that many organisms recover the greater part of their energy from anaerobic or aerobic sugar decomposition which, as is well known, generates heat. However, how the energy developed by reaction can be transferred to other processes within a cell has rarely been discussed by physiologists, as Kluyver recently pointed out. It is however clear that that part of the fermentation or respiration energy which really is developed in the form of heat within the cell is of secondary importance to the organism; the main function is played by that part which is transferred to other forms of chemical energy forms within the cell; only that part can be utilized for the synthesis and hence for reproduction, growth, and regeneration.

Generally, an energy-rich decomposition product occurring in the energy-yielding reaction must be involved in the energy-absorbing reaction.

Apart from the enzymatic couplings which we take as a basis for the phosphorylation process, we find *another coupled reaction* within carbohydrate

metabolism biochemistry, and this is linked up with a problem no less important to enzyme research, namely the relationship between anaerobic and aerobic sugar metabolism. Meyerhof has shown that the relationship between anaerobic and oxidative decomposition is the same in muscle and in yeast. On the assumption that sugar decomposition in the animal organism and in yeast takes place by way of glycogen, and on the assumption of an introductory dismutation between two different sugar residues, we have acquired an idea of the fate of sugar during oxidation[3]. The decomposition does not take place as was previously assumed in such a manner that a sugar molecule is oxidized to 6 CO_2 – this would be burning of little use to the organism – but in such manner that each hexose molecule produces one molecule CO_2, one molecule having 2 C-atoms, and the residue having 3 C-atoms. Thus in the decomposition of 6 molecules of zymohexose 6 CO_2 are formed, and from 6 $C_3H_6O_3$ residues there are again formed 3 molecules of a hexose which come into the carbohydrate reserve, and also 6 molecules of acetaldehyde disappear which provide the C-material and the energy for the cell syntheses. The following diagrammatic representation does not take into account the by-reactions owing to which the $CO_2/C_6H_{12}O_6$ ratio frequently differs considerably from the value 1.



It remains for me to mention briefly our chemical researches in connection with *cozymase*.

The reason for our doing so much work on the purification and determination of the constitution of this substance is that cozymase is one of the most

widespread and biologically most important activators within the plant and animal world.

It is only in a few microorganisms that no cozymase has been found. Its presence in lactic-acid bacteria, as found by A. Virtanen, is particularly interesting. In a recent examination, Dr. Ernst Sym and Assistant Professor Ragnar Nilsson have found that the majority of tissues and organs with high carbohydrate metabolism are particularly rich in cozymase, e.g., in addition to the working muscle, the retina and cerebral grey matter.

The difficulty in isolating cozymase is above all due to its considerable dilution. Yeast has proved the most suitable starting material despite the fact that in the most favourable cases 1 kg of yeast did not yield more than 2 cg.

By a long series of purification processes a preparation was obtained with a maximum activity – expressed in rational units – of ACo = 85,000, the starting material being characterized by ACo = 200. It was possible to convert this preparation into salts – salts of the alkaloids and of the alkaline-earth metals were used for the isolation – and cozymase can be recovered therefrom with practically unchanged activity[4]. The composition of the most highly purified product corresponds approximately to a so-called nucleotide, for it contains a sugar residue, a purine residue and phosphoric acid, and everything points to a close relationship with a substance occurring in muscle in small quantities, *adenylic acid*. In a preparation with an activity ACo = 70,000 recently prepared by Associate Professor K. Myrbäck, the ratio of adenine: reducing sugar group: phosphoric acid was found to be very close to 1. The relative molecule concentrations were, in fact[5]:

adenine	0.208
reducing sugar	0.204
PO_4	0.212

The relationship between adenylic acid and cozymase offers special interest since G. Embden in new interesting work has shown that the ammonia liberated in the muscle originates – at least largely – from adenylic acid. Attempts to prove a connection between the state of the muscle and the co-enzyme content have not given clear result yet[6], but are to be repeated with special reference to the oxygen supply whereby cozymase possibly acts as a link between the energy-producing glycolysis and the energy-absorbing synthesis.

The coenzymes, of which cozymase is the most important representative, constitute one type of the large group of *biocatalysts* which include not only enzymes but also certain hormones, growth factors, and vitamins. Of no less interest is the fact that the chemical results hitherto available point to a rela-

tionship between cozymase and many other factors essential for life, viz., the vitamins B_1 and B_2 which have been thoroughly studied particularly in England by Miss Harriette Chick and R. A. Peters, and in America by Levene, and also Wildier's « bios » and finally our factor Z.

Another group of biocatalysts distributed throughout all organisms and even in yeast fungi is the group which effects the actual oxidation, hence the final stage of respiration (C.A. MacMunn; D. Keilin; O. Warburg). Substances very closely related to haemin, the characteristic blood-pigment constituent, are found in aerobically living cells of the plant and animal world. The porphyrin residue, combined with the iron atom in these substances, belongs to a group to a knowledge of which a very progressive contribution has been made in recent years by Hans Fischer. It is interesting that an enzyme which undoubtedly participates in the respiration process, viz. *catalase*, also contains a haemin residue[7].

In addition to this *chemical* method, enzyme research is also advancing in another direction towards biology. The first problem here is the relationship of the enzyme to plasma and to the living cell.

Twenty-three years ago E. Buchner was awarded the Nobel Prize in Chemistry for the discovery that fermentation occurs in a practically cell-free « Pressaft »*. The question frequently raised since then is to what extent the enzyme complex present in Buchner's extract participates in the activity of the living cell. In more recent work in this direction use has been made mainly of so-called dried yeast.

It was principally important to determine as exactly as possible a difference between such a dried-yeast and fresh-yeast cells, particularly with reference to its power of fermentation and to its reproduction potency. In an examination carried out together with Professor Chr. Barthel[8], it was found that after treatment with alcohol and ether a dried yeast contains less than 0.1 % cells capable of reproduction, but had practically the same fermentation power as the fresh yeast; the fermentation enzymes were therefore retained in the dry cells freed of lipoids but a catalyst participating in the reproduction process was destroyed. The fact that such a dry yeast – in opposition to the fresh yeast – is completely insensitive to toluene can hardly be explained otherwise than by the assumption that the enzyme system in the living cell is combined with the protoplasm and dependent on the structure thereof. In connection with these structural changes there arises a problem of even more general

* Juice extracted by Buchner from yeast cells by compression with a hydraulic press.

scope, viz., the existence of transitions between enzymes and living matter.

In addition to certain facts found in the study of dry yeast, the properties of bacteriophages and particularly of plant virus as it occurs in certain chlorophyll diseases, point to the existence of enzyme-like substances, *enzymoids*, which are distinguished from the actual enzymes by their power of reproduction.

In many fields of biology which were hitherto treated mainly descriptively, new and exact questions can be put by enzymochemical thought processes and methods.

As a first example I will take the *science of adaptation*.

When the individual adapts himself to changes in nutritional conditions, changes in temperature, and so on, the first measure of the organism is to develop the enzyme system necessary and appropriate to the new conditions. Under normal conditions – as we have been able to show in the case of yeast – this is surprisingly constant, but under certain culture conditions enzymes, for example saccharase, may develop to ten times the normal amount.

I think that the *sciences of immunity* and *heredity* are in particular the fields in which we may expect new discoveries by the application of enzyme chemistry.

With regard to immunity research, the analogies found between the enzyme activator–substrate system on the one hand and the complement–amboceptor–substrate system on the other hand are all the more obvious. Since purification and characterization of the enzymes and activators have provided the preconditions to more detailed study of enzymatic processes, there is even reason to begin the study of antigens and antibodies by purification and concentration.

Heretofore it has not been possible to bring into contact with chemical facts the extremely interesting results of genetics, which have led to a very exact but purely formal determination of hereditary units (genes). Although many years of work in many fields will be required to obtain a link between genetics and biochemistry, no geneticist will have any doubts concerning the need for such work. Our researches are aimed at finding the lines of development of chemical substances in mutants subject to Mendel's law. Independently of current hypotheses (R. Goldschmidt *inter alia*), a search should be made into the origin of such lines of development in substances of an enzymoid nature.

Investigation of the enzymes and biocatalysts means a step forward to an understanding of Life on the chemical and physical basis. But although an accurate knowledge of the chemical processes of life is a precondition to an understanding of life phenomena, and although the laws discovered for in-

animate matter must apply fully and strictly to living matter as well, I nevertheless think that it is rash to assert that our laws concerning transmutation of matter and the conversion of energy are sufficient to describe the life phenomena.

The more we are able to follow and see through the chemical and physical phenomena whereby organisms maintain their individual life in the face of external influences and preserve the race by reproduction, the more we can hope to advance to the knowledge of the great principle which together with the laws of conservation of matter and energy, and of the decrease in free energy, govern organic life. The knowledge of this principle and its clear formulation is one of the highest scientific purposes of natural science, biology and biochemistry in the first instance.

I must express my sincere and respectful thanks to the Royal Academy of Sciences of Sweden for the extended possibilities afforded to myself by the Nobel Prize to continue my biochemical research.

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2. H. von Euler and K. Myrbäck, *Hoppe-Seylers Z. Physiol. Chem.*, 181 (1929).
3. H. von Euler, *Arkiv Kemi*, 9, No. 44 (1927).
4. H. von Euler and K. Myrbäck, *Hoppe-Seylers Z. Physiol. Chem.*, 184 (1929).
5. H. von Euler and K. Myrbäck, *Hoppe-Seylers Z. Physiol. Chem.*, 189 (1930).
6. E. Sym, R. Nilsson, and H. von Euler, *Hoppe-Seylers Z. Physiol. Chem.*, 189 (1930).
7. H. von Euler, K. Zeile, and H. Hellström, *Svensk Kem. Tidskr.*, 42 (1930).
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Biography

Hans von Euler-Chelpin was born on February 15, 1873, at Augsburg. His father, who was then a captain in the Royal Bavarian Regiment, was transferred to Munich and von Euler-Chelpin spent most of his childhood not far away with his grandmother at Wasserburg. After going to school at Munich, Wurzburg and Ulm, he studied art from 1891 until 1893 at the Munich Academy of Painting, first under Schmid-Reutte and later under Lenbach, whose gifted and powerful personality greatly influenced him. His desire to study problems of colour and especially the colour of the spectrum led von Euler-Chelpin to begin, in 1893, the study of science.

He therefore went to the University of Berlin to study chemistry under Emil Fischer and A. Rosenheim, and physics under E. Warburg and Max Planck; and in 1895 he took his doctorate at the University of Berlin.

He then took a short course in physical chemistry in Berlin and went, after this, to the University of Göttingen to work from 1896 until 1897 under W. Nernst. In the summer of 1897 he went to work in the laboratory of Svante Arrhenius in Stockholm and was appointed assistant there. In 1898 he qualified as Privatdozent in physical chemistry in the Royal University at Stockholm, and in 1899 he was appointed as such in that University. Between 1899 and 1900 he visited the laboratory of Van 't Hoff. Both Van 't Hoff and Nernst greatly influenced his scientific development.

Subsequently, visits to the laboratories of A. Hantzsch and J. Thiele confirmed his interest in organic chemistry and he then began to work on this subject, partly in collaboration with Astrid Cleve, who was his wife at that time. During this period he visited the laboratories of E. Buchner in Berlin and G. Bertrand at the Pasteur Institute in Paris.

In 1906 he was appointed Professor of General and Organic Chemistry in the Royal University, Stockholm. In 1929 the Knut and Alice Wallenberg Foundation and the International Education Board of the Rockefeller Foundation established in Stockholm the Vitamin Institute and Institute of Biochemistry, and von Euler-Chelpin was appointed as its Director. In 1941 he retired from teaching, but continued his researches.

Von Euler-Chelpin's first biochemical work was published in 1904. Its subject was the action of enzymes considered in relation to his earlier work on catalysis. This earlier work had won him, in 1898, the Lindblom Prize of the German Academy of Sciences for a paper on the catalytic hydrolysis of substrates by salt formation with the catalyst, work which he later developed further in collaboration with E. Rudberg and A. Ölander. From 1906 onwards, von Euler-Chelpin was chiefly concerned with physico-chemical and biochemical problems, publishing, from 1908 to 1909, the results of his work on the chemistry of plants, and in 1915 the results of his collaboration with P. Lindner on the chemistry of the fungi. From 1925 until 1930 he worked on the chemistry of enzymes.

An important part of von Euler-Chelpin's work was done in collaboration with K. Josephson on the enzymes saccharase and catalase. The work he had begun in 1905 on fermentation was specialized in his Institute to phosphorylation, and the first phases of fermentation and their catalysis were studied, with special attention to co-zymase and also related activators. In this latter work K. Myrbäck played a great part. An important result of his work with his collaborators on co-zymase was his clarification of its structure, other conclusions being confirmed by Lord Todd in 1956.

In 1924 von Euler-Chelpin began his numerous studies of the vitamins in collaboration with B. von Euler, Paul Karrer and Margareta Rydbom, with whom he carried out, in 1928, a study of the marked vitamin A activity of carotene. His work on fermentation and general enzyme chemistry was continued in the Institute established in Stockholm by the Wallenberg and Rockefeller Foundations, special attention being given to the use of enzyme chemistry for the study of heredity and the blood serum.

In 1929 von Euler-Chelpin was awarded jointly with Arthur Harden, the Nobel Prize for Chemistry for his work on alcoholic fermentation. In 1914 he had published a book on the chemistry of yeast and alcoholic fermentation. Between 1925 and 1934 he embodied the results of his very extensive research in enzymology in his monograph entitled *Chemie der Enzyme*, which was the first modern monograph on this subject. In 1957 he published with B. Eistert a book on the chemistry and biochemistry of reductones. With C. Martius he had succeeded in preparing triose-reductone. In 1958 he visited Japan and published a monograph on the reductones in collaboration with Professor K. Yamafuji and Drs. Namura and Adachi.

Later in 1935 von Euler-Chelpin investigated the biochemistry of tumours and especially studied the nucleic acids in tumours by means of labelled

compounds by a technique he invented in collaboration with G. de Hevesy. On tumours he published two important monographs, one entitled the *Biochemistry of Tumours*, written in collaboration with Boleslaw Skarzynski of Cracow and published in 1942 and the other entitled *The Chemotherapy and Prophylaxis of Cancer*, published in 1962.

A careful teacher and a friend to all who worked with him, von Euler-Chelpin has inspired and exerted great influence on many workers in the field of biochemistry.

He was a Fellow of the Academies of Sciences of Bangalore, Berlin, Munich, Rome, Paris, Vienna, Copenhagen, Helsinki, Moscow, Leningrad, Halle, Göttingen, Tokio and New Delhi. He was a Member of the Royal Swedish Academy of Sciences, the Royal Swedish Academy of Engineering Sciences, the Royal Institution, London, the Finnish Academy of Sciences, and the Academy of Sciences of New Delhi, a Foreign Member of the Max Planck Society, a Corresponding Member of the Academy of Sciences, Paris, and an honorary member of the Academies of Sciences of Helsinki and Japan, the Indian Academy of Sciences, the Chemical Societies of France, Italy and Berlin, and of the Japanese Cancer Association, Tokio. He held honorary doctorates of the Universities of Stockholm, Zurich, Athens, Kiel, Berne, Turin, and Rutgers and New Brunswick Universities. In 1959, he was awarded the Grand Cross for Federal Services with Star, Germany.

Von Euler-Chelpin married twice. His first wife, Astrid Cleve, is mentioned above. In 1913 he married Elisabeth Baroness af Ugglas, who collaborated with him in his work. There were nine children by this marriage.

He died in Stockholm on November 6, 1964, at the age of 91.

Chemistry 1930

HANS FISCHER

«for his researches into the constitution of haemin and chlorophyll and especially for his synthesis of haemin»

Chemistry 1930

Presentation Speech by Professor H. G. Söderbaum, Chairman of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

« Blood is a very special liquid », this was asserted some 140 years ago by Goethe. When writing these words and ascribing them to Mephistopheles he probably had in mind first and foremost the mystical aura with which popular superstition has been wont to invest since time immemorial the red river of life that flows in our blood vessels, and the magical forces with which it had long been held to be endowed. The methodical scientific research of a later age has however affirmed the phrase to a far greater degree than its author could have surmised. Many and difficult have been the riddles scientists have had to solve in research on blood. The number of those who have applied their ingenuity to the solution of the riddle is large. It is the privilege of this present generation to witness the raising of the veil of Isis which previously concealed the solution from view. The research to which the Academy of Sciences has felt itself constrained to award the Nobel Prize for Chemistry this year is exceptionally successful and significant.

Once the anatomists of the 17th century had demonstrated with the aid of the microscope that blood is a tissue – in the anatomical sense of the word – and that it consists partly of extremely small cells, the so-called blood corpuscles, partly of a liquid substance, the so-called plasma, it became the task of the chemists and physiologists to determine the composition of these constituents and their diverse functions in the vital process. As to the red blood corpuscles in particular it was found that their colour is due to an iron-containing substance, later called haemoglobin, which, by virtue of its strong affinity to oxygen, is of fundamental importance for the familiar changes venous blood undergoes in the lungs during respiration. Haemoglobin can be separated into a protein substance, i.e. globin, and a red substance, still containing iron which, after oxidation, with hydrochloric acid yields a salt-like complex iron compound, called haemin. Considerable uncertainty however prevailed for a long time even regarding the empirical formula of haemin, and the uncertainty as to its internal chemical structure was even greater. Elementary analysis showed that the haemin molecule contains a large num-

ber of carbon atoms (the data fluctuated between 32 and 34) and an almost equal number of hydrogen atoms, and also 4 oxygen atoms, 4 nitrogen atoms, 1 iron atom, and 1 chlorine atom. To determine the manner in which all these atoms, numbering more than 70, are linked, or in other words to determine the chemical constitution of haemin, was one of the most difficult and complicated tasks with which any chemist could be faced.

It was discovered that the haemin molecule can be converted by certain chemical procedures into iron-free substances, called porphyrins, and that the porphyrins can be broken down, by other procedures, into pyrrole derivatives, i.e. into compounds containing four carbon atoms and one nitrogen atom in a closed ring. It was clear that the road to an exact knowledge of the structure of the blood pigments would involve detailed examination of these pyrroles and porphyrins.

This is the road which Professor Hans Fischer of Munich travelled, to reach his destination with perseverance and determination; not only did he determine completely the constitution of haemin and all its decomposition products: he also prepared the blood pigments from their simplest constituents by synthesis, a scientific achievement which would scarcely have been considered possible even a generation ago. By this synthesis he crowned his researches which both in extent and in the unbelievable difficulties associated with them deserve to be called a gigantic labour.

Moreover, these researches were not wholly restricted to blood pigments. Closely related pigments occur in Nature and not only in the blood. These include the pigments in the bile, of which bilirubin is the best characterized to date. Its constitution, too, has been determined by Fischer who established the connection between this bile pigment and the blood pigment. Further, it was discovered that the pigment in the pinions of certain birds is the copper salt of a porphyrin, whereas the pigment which forms the dark spots on the eggs of a large number of wild birds, the so-called ooporphyrin, has been found to be blood pigment without iron. Even if I add that Fischer has demonstrated the occurrence of haemin in yeast, all this is overshadowed by the fact that, chemically speaking, the pigment of green plants, i.e. chlorophyll, is closely related with the red blood pigment, and even derives, as Fischer has shown, from exactly the same parent substance, as regards the porphyrins.

This shows that Nature in spite of her extravagant diversity was sufficiently economical to use exactly the same building material when constructing these two substances which are so greatly different in appearance and occurrence.

Having completed his work on the blood pigments and their components by the haemin synthesis, Fischer turned with undiminished energy to research into chlorophyll. In this field, where a scientist has previously gained a Nobel Prize, but where much work remained to be done, conditions are even more complicated and the difficulties as a consequence are even greater than in the other field. Nevertheless, Fischer obtained results which are so important that the Academy has considered it fitting to include them in the award.

What has been said, though necessarily brief, could give some idea of the variety and range of Fischer's researches, and has shown at the same time the singlemindedness that prevails in all this variety in that a leading fundamental idea firmly combines the researches in a systematic whole.

These researches have in the main been concerned as we have seen with the two most vital pigments, haemin and chlorophyll. Almost, we are tempted to say that life is pigment, because oxygen transport, by means of blood pigment, to the various tissues of the bodies of animals and humans, and carbon dioxide assimilation in plants, due to chlorophyll, constitute two of the most fundamental processes of organic life. It is therefore hardly possible to overestimate the importance of detailed knowledge of these two vital factors. If we remember moreover that the pyrrole complexes determined by Fischer are contained as basic components partly in the principal catalysts of respiration, partly in an enzyme (catalase) which is indispensable to all living cells, it will be found that the intrinsic value of the researches on it is in full accord with the prize which will now be awarded.

Herr Geheimrat Fischer. The gold medal which you are about to receive shows, on the obverse, the figure of Science, unveiling the goddess Isis. The symbol seems to me particularly appropriate on the present occasion, because you yourself, dear colleague, have solved previously veiled secrets of Nature in exactly the same manner.

By your analytical and synthetic work on the porphyrins, on the blood pigment, on leaf pigments, and other related substances, you have accomplished an achievement which can only be described a great feat in chemistry which will undoubtedly have a beneficial effect on the most diverse branches of natural sciences.

To have mastered a multitude of individual results so successfully testifies not only to untiring, I am tempted to say indefatigable energy, and to superior experimental ability, but also to a rare determination and consistency of scientific thought, which is rivalled by few examples in the history of our science.

In gratitude for your achievement, and with cordial congratulations, I now ask you, in the name of our Academy of Sciences, to receive, from the hands of His Majesty the King, the Nobel Prize in Chemistry for the year 1930.

Hans Fischer

On haemin and the relationships between haemin and chlorophyll

Nobel Lecture, December 11, 1930

The Swedish Academy of Sciences has awarded to me the Nobel Prize for my investigations into blood and leaf pigments and for the synthetic preparation of haemin, and I therefore wish to report my results, in so far as this can be done in a brief lecture.

The blood pigment haemoglobin is a compound which can be split by diverse methods into its constituents, pigment and protein. Teichmann was the first to observe this cleavage under the microscope when he subjected blood to the effect of glacial acetic acid – common salt; Schalfejeff, Nencki, Piloty, Willstätter and others have used the method on a large scale, so that Teichmann's crystals are available by the kg. The Swedish scientist Mörner has also developed a method for effecting separation with the aid of alcohol – sulphuric acid, by means of which esters of haemin are obtained.

Haemin has the formula $C_{34}H_{32}O_4N_4FeCl$. Countless variations of this atomic arrangement are possible. By analytical methods of Nencki, Küster, Piloty, Willstätter, H. Fischer and their pupils, the pyrrole nature of the haemin was demonstrated, and much information was obtained about its constitution. When haemin is deprived of its iron, porphyrins are formed, which are substances having a sensitizing effect, as Hausmann has shown.

These porphyrins are widely distributed in Nature, and it was possible to assume as a working hypothesis from the start that there existed a relationship with the porphyrins of blood pigment; it was moreover to be expected that the determination of their constitution would also provide information about the constitution of haemin itself, just as the results of distintegration of bilirubin which is formed from blood pigment by biological means had stimulated determination of the constitution of blood pigment itself. This was the reason why I tackled systematically the investigation of natural porphyrins, and the biological degradation of blood pigment itself.

In cases of porphyria, a minor disease, the patient excretes large quantities of porphyrins. Previously, it was assumed that haematoporphyrin was involved; this view could be refuted. At least two porphyrins are excreted, uro-

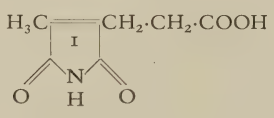
and coproporphyrin, both of which occur in the urine – one of the two, probably coproporphyrin, had been observed already by Hammarsten in a case of sulfonal poisoning –, although, quantitatively, most of the coproporphyrin occurs in the faeces. It is not always the same coproporphyrin that is present in the urine. Hijmans van den Bergh observed an isomeric coproporphyrin, admittedly only in a case of porphyria as yet. It is interesting to note that uroporphyrin also occurs in the pinions of African birds, in species of *Turacus*, in the form of a complex copper salt.

Closely related to uroporphyrin is conchoporphyrin which is present in seashells, probably in the form of calcium salt.

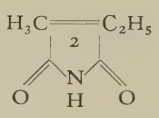
Coproporphyrin in particular is widespread; traces are present in normal urine, and also in yeast. In special cultures, yeast can be made to produce considerable quantities of coproporphyrin. The yeast is then brought to a condition which can be compared with porphyria in humans.

A porphyrin (ooporphyrin) is also contained in the spots on the eggs of birds incubating out of doors. Putrefaction of blood pigment produces a porphyrin identical with the above, Kämmerer's porphyrin; protracted putrefaction produces deuteroporphyrin.

In turning to a discussion of the determination of the constitution of haemin itself, I can of course only give a brief report of the most important results obtained in these investigations which extended over decades. The starting point was W. Küster's observation of the oxidative formation of haematinic acid (1) which, on decarboxylation, yielded methylethylmaleinimide (2):



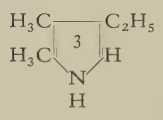
Haematinic acid



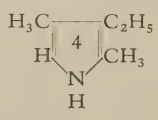
Methylethylmaleinimide

Reductive cleavage of the haemin yielded the following pyrrole derivatives of basic and acid nature:

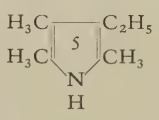
Haemopyrrole bases



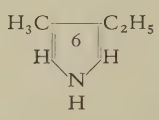
Haemopyrrole



Cryptopyrrole

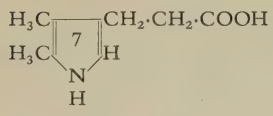


Phyllopyrrole

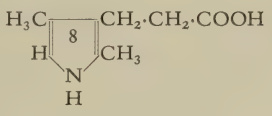


Opsopyrrole

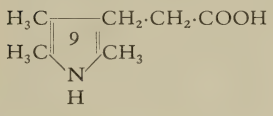
Haemopyrrolic acids



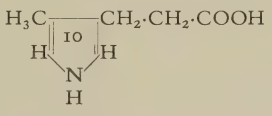
Haemopyrrole carboxylic acid



Cryptopyrrole carboxylic acid



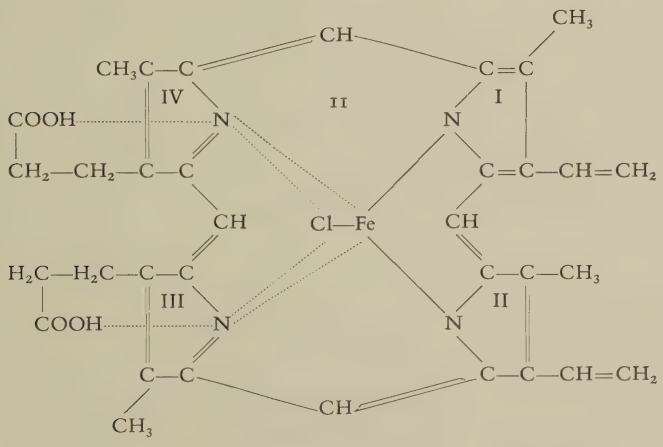
Phyllopyrrole carboxylic acid



Opsopyrrole carboxylic acid

During oxidation, the acid components yield Küster's haematinic acid, the basic constituents, methylethylmaleinimide. This established the principal features of their constitution; exact proof is provided by syntheses which we shall not discuss in detail. These syntheses rendered these products available in any desired quantities. The yield of bases and acids from haemin is so substantial as to suggest that there are four pyrrole nuclei in the molecule, which agrees with molecular weight determination.

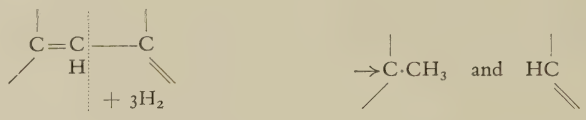
As early as 1912, W. Küster derived a constitutional formula for haemin which on the whole presents an accurate picture of haemin. We reproduce the formula as it has now been proved by synthesis; in reviewing the analytical results, we shall trace the logical, not the historical development.



Four pyrrole nuclei (more accurately: 1 pyrrole-, 1 maleinimide-, and 2 pyrrolenine-rings) are linked by four methin groups. The consecutive sequence

of simple and double bonds dictates the colour. The FeCl group has entered the molecule complex, substituting two NH groups.

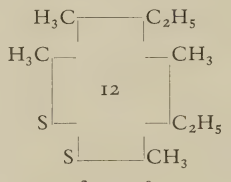
By reductive cleavage at the methin groups, a methyl residue and a free methin group are formed,



resulting in the mixture of pyrroles 3–10.

The methin groups are oxidized out by oxidative cleavage, and haematinic acid is obtained in a yield which corresponds to two pyrrole nuclei (III and IV). The base fraction (I and II) is evidently totally destroyed, which is explained by the vinyl groups at which oxidation is initiated.

If haemin is subjected to mild reduction with hydrogen iodide according to Nencki, we obtain mesoporphyrin (12). To simplify the extensive formula (see above) we omit the four methin groups and the lower half of the four pyrrole nuclei, indicate only the upper half of the pyrrole nucleus by a square bracket with the associated β-substituents; the propionic acids residue $CH_2 \cdot CH_2 \cdot COOH$ we abbreviate by the Latin letter « S ».

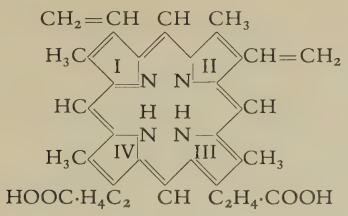


f.p. 212°.

$(C_{34}H_{38}N_4O_4)$

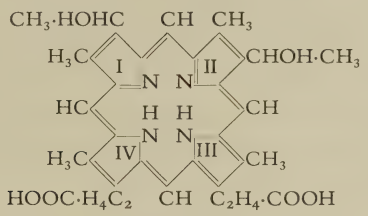
If we reduce haemin catalytically, we obtain mesohaemin, and in both cases the unsaturated side chains, i.e. the vinyl groups, are converted into ethyl residues, because, during oxidation, there is now formed methylethylmaleinimide, which we missed before, two molecules methylethylmaleinimide (2) and two molecules haematinic acid (1) being formed.

If haemin is deprived of its complexly bound iron, preferably with ferric formate we obtain proto- of Kämmerer's porphyrin:



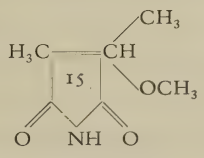
$(C_{34}H_{34}N_4O_4)$ (13)

Only the complexly bound iron is removed, because, conversely, this porphyrin can again be converted into haemin. If, for iron separation according to Nencki, we use acetic acid – hydrogen bromide, hydrogen bromide will at first be added to the unsaturated side chains of haemin, as Willstätter observed, and hydrolysis occurs subsequently, so that haematoporphyrin is formed:



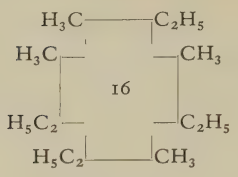
$(C_{34}H_{38}N_4O_6)$ (14)

In this, two molecules water are added to the two vinyl groups (nucleus I and II) of the protoporphyrin, so that hydroxyethyl residues have formed. Again, on oxidation, haematoporphyrin only yields haematinic acid, because the basic fraction is destroyed, starting with the hydroxyethyl residues. If these hydroxyethyl residues are however stabilized by etherification, as Küster did in the case of tetramethylhaematoporphyrin, there are obtained, by oxidation, apart from two mol haematinic acid, two mol of the imide having the following constitution:



Imide f.p.64°

If we decarboxylate mesoporphyrin, we obtain, under evolution of carbon dioxide, the oxygen-free aetioporphyrin:



$(C_{32}H_{38}N_4)$

Chlorophyll can in the end be broken down into two aetioporphyrins, pyrroporphyrin ($C_{30}H_{34}N_4$) and phylloaetioporphyrin ($C_{31}H_{36}N_4$) which cannot be obtained from blood pigment, but both of which represent secondary conversion products of chlorophyll.

On the constitution of natural porphyrins

Ooporphyrin is identical with protoporphyrin or Kämmerer's porphyrin. If we introduce iron complexly into ooporphyrin, we obtain haemin. If we reduce ooporphyrin ester with hydrogen iodide, we obtain mesoporphyrin, and the ester mentioned can also be converted into tetramethylhaematoporphyrin and haematoporphyrin. The following diagram illustrates these conversions which are in part reversible:

mesoporphyrin

↑

tetramethylhaematoporphyrin ⇄ ooporphyrin ester ⇄ haematoporphyrin

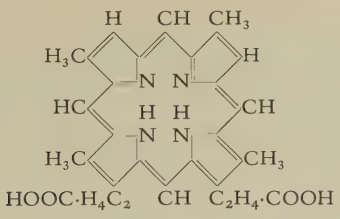
⇅

haemin ester

Ooporphyrin therefore is haemin without the iron.

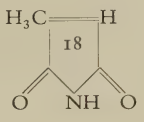
These reactions with ooporphyrin from egg-shells constituted partial synthesis of haemin and provided much information about its constitution. The haemin synthesis which was later carried out was based on these observations.

In short-term haemoglobin putrefaction, it is only the complexly bound iron which is separated apart from globin, and Kämmerer's porphyrin forms, which can be reconverted into haemin. In protracted putrefaction of haemoglobin for several months with sodium carbonate, the unsaturated side chains of haemin are separated, and deuterohaemin forms. The complexly bound iron is therefore substantially preserved. From deuterohaemin, we obtain the iron-free deuteroporphyrin by splitting off the iron.

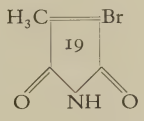


(17)

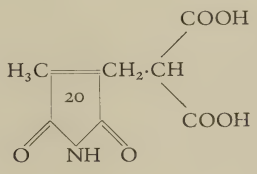
This is proved by isolation of citraconimide (18)



by oxidation apart from haematinic acid, further by bromination, which yields dibromodeuteroporphyrin, and by oxidation of dibromodeuteroporphyrin which leads to the formation of bromocitraconimide (19) apart from haematinic acid:

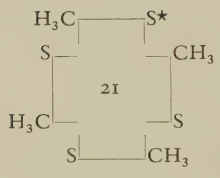


On oxidation, uroporphyrin yields carboxylated haematinic acid (20), coproporphyrin yields haematinic acid (1).

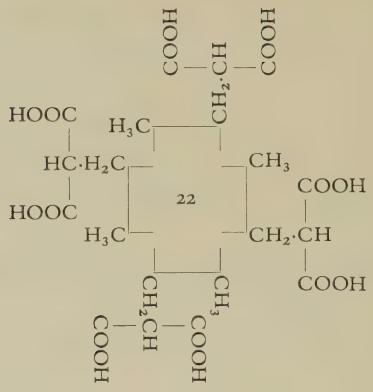


On reduction, coproporphyrin yields exclusively haemopyrrolecarboxylic acid (7).

The base fraction is absent, so that coproporphyrin most probably represents a mesoporphyrin containing propionic acid residues in the place of the two ethyl residues, whereas uroporphyrin would then represent the corresponding « malonic acid ». The following formulae correspond to these relationships:



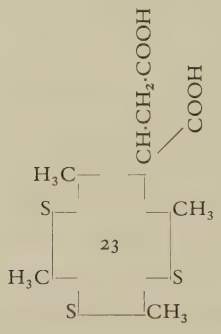
Coproporhyrin



Uroporhyrin

This is in harmony with the decarboxylation of the two pigments which leads to aetioporphyrin; from this we can draw conclusions as to the presence of four methyl and four ethyl groups in aetioporphyrin. The decarboxylation reaction in the natural porphyrins was exceptionally smooth; for the first time we obtained an aetioporphyrin in the characteristic butterfly crystal shapes, which determined the establishment of the relationships between the synthetic aetioporphyrins, to be described later, and the analytical aetioporphyrin.

In mother-of-pearl shells, conchoporphyrin was discovered, which is a monocarboxylated coproporphyrin which yields a pentamethylester, and which probably has the following constitutional formula:



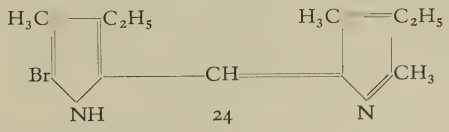
This formula contains a succinic acid residue as a side chain. Recent synthetic results suggest that uroporphyrin also contains two succinic acid residues, because a synthetically prepared porphin-octacarboxylic acid was found to be non-identical with uroporphyrin.

* S = $CH_2 \cdot CH_2 \cdot COOH$.

Synthetic results

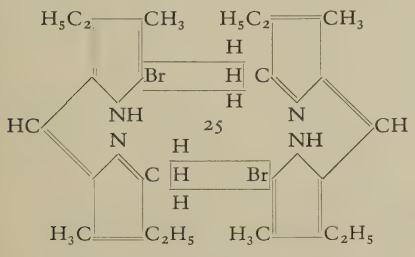
Different views have been put forward about the constitution of haemin and aetioporphyrin. Apart from Küster's view, it was above all the constitution of a tetrapyrrylethylene, as put forward by Willstätter (see Willstätter's Nobel Lecture on June 3, 1920, p. 9: *Les Prix Nobel en 1914–1918*), and the possibility of combining the two formulae, which were under discussion. The methods of synthesis had to be applied systematically in this field; this was however opposed by the relatively slight development of pyrrole chemistry, only cryptopyrrole having been prepared synthetically among the reductive cleavage products of blood pigment and bile pigment, and the yields were so small that the systematic development of pyrrole pigments was out of the question. One after another, all the cleavage products of blood pigment were however prepared synthetically, and the methods were perfected so that these pyrroles are now available for synthetic purposes in any desired quantity.

Inter alia, the action of bromine on cryptopyrrole leads to a magnificent brominated methene which possesses the following constitutional formula:

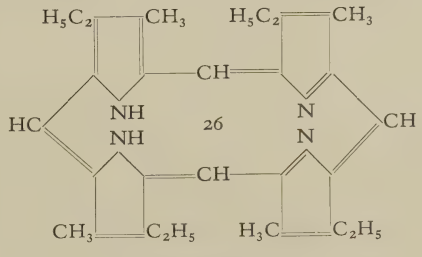


This formula has been established by synthesis, and it has become fairly common to convert tri-substituted pyrroles into methenes of this type by means of bromine. (Frequently, bromine also enters in the α′-methyl group. These methenes are distinguished by exceptionally easy conversion into porphyrins.)

On being treated with acids, in particular on boiling with formic acid, the above methene yielded aetioporphyrin. The reaction is due to the combination of two molecules of the methene, separation of hydrogen bromide, and dehydrogenation according to the following formula:

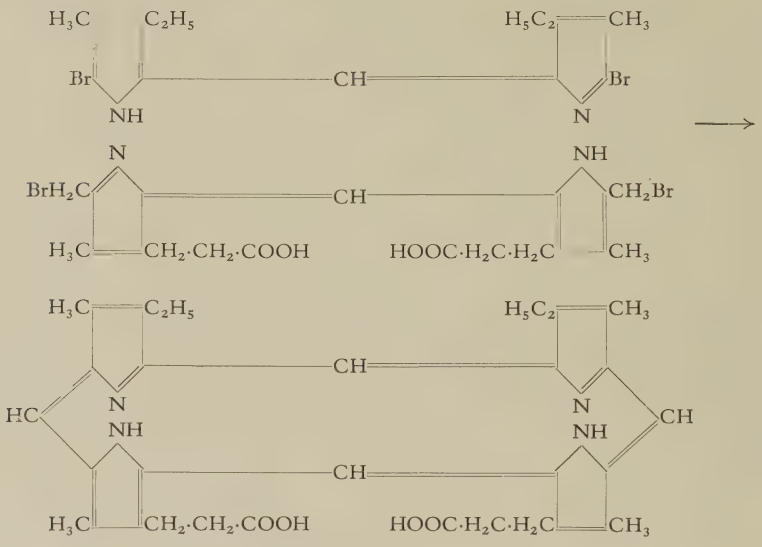


Bromo-methene from cryptopyrrole



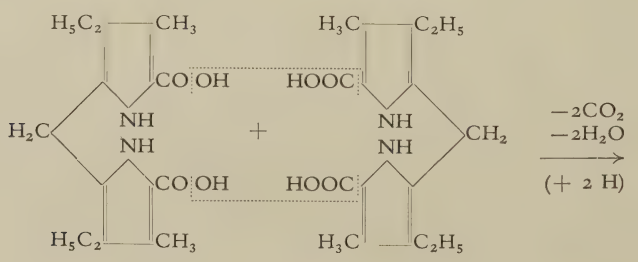
Aetioporphyrin I

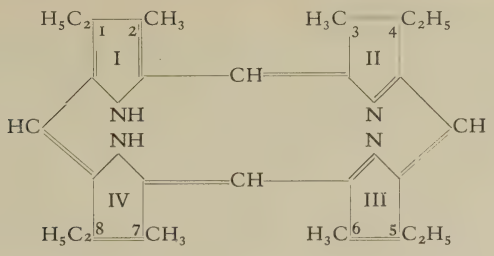
From the point of view of preparation, particular significance attaches to the synthesis from dinuclear-brominated dipyrrylmethenes and methylbrominated dipyrrylmethenes, which synthesis is represented by the following diagram:



which also supports the view of the constitution of aetioporphyrin and of the porphyrins in general in accordance with Küster's old formula.

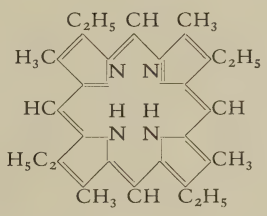
Porphyrin synthesis from mononuclear-brominated methenes by condensation of two molecules can also be applied to diverse methenes, and, in one of the two methenes, a free α-methin group may take the place of nuclear bromine. This synthesis has proved itself in particular for porphinmonopropionic acids. With a good yield, porphyrin synthesis can also be effected from methane dicarboxylic acids, preferably by heating with formid acid, when the leuco compound will first form at 40° with vigorous carbon dioxide evolution, and will then be converted into porphyrin.



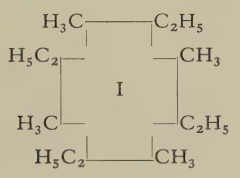


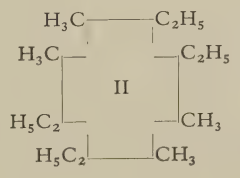
The blood pigment cleavage products opsopyrrole 6 and opsopyrrole carboxylic acid 10, which possess two free methin groups were converted into porphyrins under the effect of formic acid and formaldehyde (methyl chloride in ether is also very suitable), and this synthesis again proves the presence of four methin groups in the porphyrins and consequently in haemin.

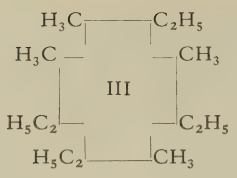
These syntheses prove the correctness of Küster's formula; there are four methin groups which link four pyrrole nuclei, and aetioporphyrin is expressed by the following formula:

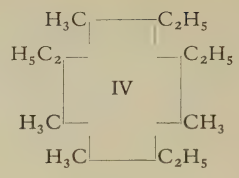


If, in this formula, we imagine the methyl and ethyl residues to be replaced by hydrogen, we obtain *porphin* on which all porphyrins are based. If we introduce four methyl and four ethyl residues into this system, we obtain, conversely, « aetioporphyrin », but it is evident that the introduction of the four methyl and four ethyl residues can be effected in four different ways, or in other words that four different isomers are possible depending on the relative position of the methyl and ethyl residues, as follows:

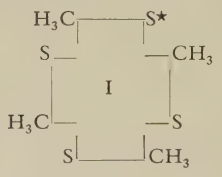


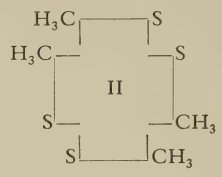


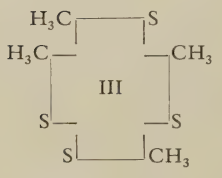


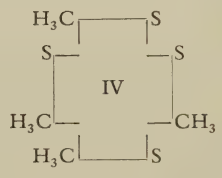


These four aetioporphyrins have been synthetized by different methods and have been found to differ. Mixed crystallization of I and II produced the typical butterfly crystal shape of aetio-uroporphyrin (see p. 172), so that a preparation identical with «natural aetioporphyrin» was obtained for the first time. The identification of the aetioporphyrins is however difficult, because they all possess high melting points. With the coproporphyrins, the situation is simpler. If we replace the ethyl residues in the aetioporphyrin by propionic acid residues, four tetramethyl-tetrapropionic acid porphins are formed, theoretically, which represent the four theoretically possible coproporphyrins:









All four coproporphyrins, which are spectroscopically identical, were in fact produced synthetically; but whereas the four aetioporphyrins melt at about 400°, the esters of the coproporphyrins are characterized by sharp melting points, so that difference or identity can easily be established. Coproporphyrin I was found to be identical with the coproporphyrin from cases of porphyria, with the coproporphyrin from yeast, and the coproporphyrin from uro- and conchoporphyrin. This proves formula No. 21 on p. 172.

On the other hand, the coproporphyrin of Hijmans van den Bergh (p. 166) was identical with coproporphyrin III (see above).

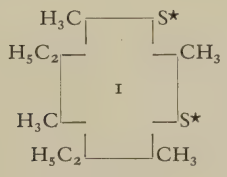
The dualism of the porphyrins which had first been recognized biologically from a study of porphyria, in particular that of yeast, had therefore been exactly demonstrated. Nature works on two different systems of reactions.

* S = $CH_2 \cdot CH_2 \cdot COOH$.

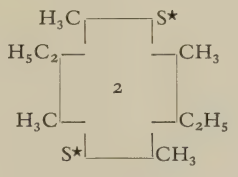
It is important to effect identification of coproporphyrin (and of course of uroporphyrin where necessary) in every case of porphyria by isolation as ester and by melting point. Whether the coproporphyrin of normal urine is III or I, remains undecided. II and IV are highly improbable.

The most important problem now was the determination of the sequence for haemin. Since haemin contains two unsaturated side chains, elucidation was exceptionally difficult, and we therefore turned to the synthesis of the mesoporphyrins, where conditions were much simpler, in particular because mesoporphyrin is a very stable substance. Analysis showed that mesoporphyrin is a tetramethyl-diethyl-dipropionic acid-porphin, and the synthesis of such porphyrins presented no difficulties; theoretically, there were however a large number of possible isomers, which are derived from the 4 aetioporphyrins in that propionic acid residues (S) replace two ethyl residues. It will be seen that two variations are possible at I, three at II, six at III, and four at IV, 15 isomers in all, which are shown in the following table

From I:

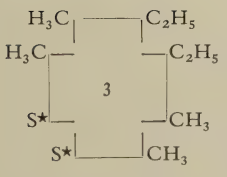


f.p. 167 or 188°

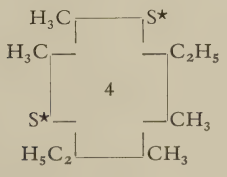


f.p. 223°

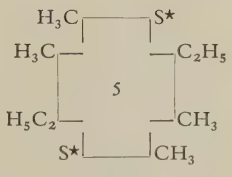
From II:



f.p. 275–278°

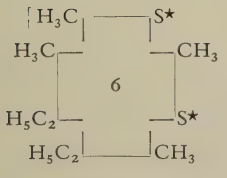


f.p. 223°

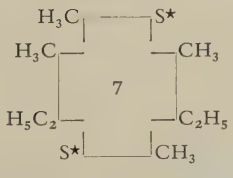


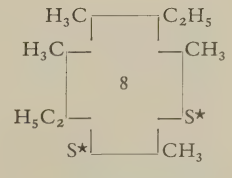
f.p. 274°

From III:

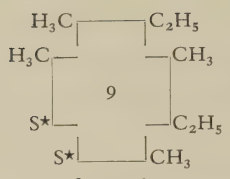


f.p. 199°

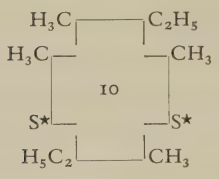


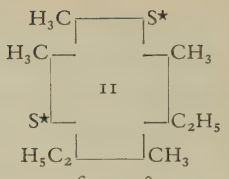


f.p. 181–183°



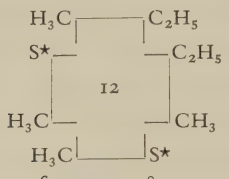
f.p. 212°



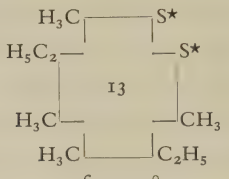


f.p. 174°

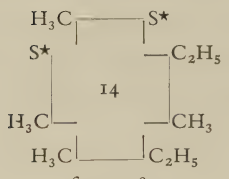
From IV:



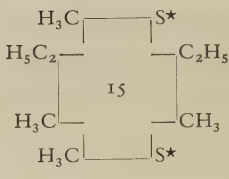
f.p. 190–191°



f.p. 217°

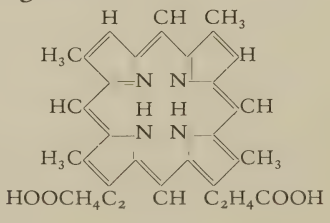


f.p. 205°



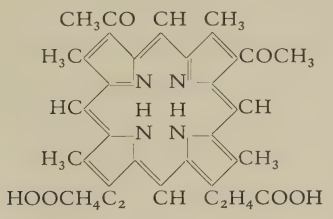
Of these fifteen mesoporphyrins, 12 were synthesized. Their dimethyl ester melting points are stated in the formulae. Mesoporphyrin 9 (see above) was found to be identical with mesoporphyrin from haemin. Since mesoporphyrin 9 is derived from aetioporphyrin III (see table), the structure of blood pigment corresponds to aetioporphyrin III. This proved the mode of arrangement of the side chains in haemin, and it became possible to embark upon systematic synthesis.

Haemin synthesis was carried out as follows. In protracted putrefaction of haemoglobin, we have repeatedly mentioned deuterohaemin or deuteroporphyrin, which lacks the unsaturated side chains of haemin. Since the unsaturated side chains of haemin are converted into ethyl residues on transition to mesoporphyrin, we obtain the formula of deuteroporphyrin if we replace the two ethyl residues in mesoporphyrin 9 by hydrogen. Deuteroporphyrin has therefore the following formula

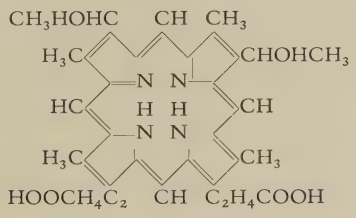


* S = $CH_2 \cdot CH_2 \cdot COOH$.

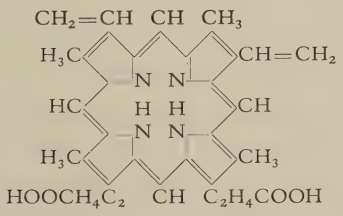
The synthesis of this substance was carried out and it was proved to be identical with deuteroporphyrin. Into its iron salt, deuterohaemin, we succeeded in introducing two acetyl residues, to form diacetyl-deuterohaemin or diacetyldeuteroporphyrin:



which on partial reduction yielded haematoporphyrin, which therefore had the following formula:



Two molecules of water could be removed from the haematoporphyrin; protoporphyrin was thus formed, which was converted into haemin by introducing iron:



According to the crystallographic investigation by Prof. Steinmetz, this haemin was shown to be wholly identical with haemin.

Proof of constitution was further complemented by synthesis of tetramethylhaematoporphyrin which on oxidation yielded imide 15 (see p. 169) with a melting point of 64°.

Once the constitution of haemin had been elucidated and it had been identified as a derivative of aetioporphyrin III, considerable interest attached to the

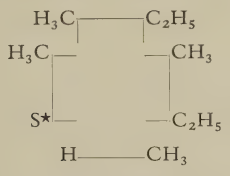
determination of the arrangement of the substituents in chlorophyll, to discover whether relationships existed with aetioporphyrin I as in the majority of the natural porphyrins, or to aetioporphyrin III, or whether an entirely different parent substance was involved. I can only mention in passing the fundamental investigations by Willstätter (cf. his Nobel Lecture and the book on chlorophyll by Willstätter and Stoll, Verlag W. Springer, Berlin 1913); I shall select from Willstätter's important results only those which contributed to the solution of the problems mentioned above or which made such a solution possible. During energetic degradation of chlorophyll with alkali, phyllo-, pyrro-, and rhodo-porphyrin are formed, from which Willstätter obtained, by pyro-reaction, an aetioporphyrin which he considered to be identical with the aetioporphyrin from blood pigment. We resumed investigation and were able to isolate from rhodo- and pyrro-porphyrin a common aetioporphyrin, which had one ethyl residue less than the aetioporphyrin from mesoporphyrin. Phylloporphyrin yielded an aetioporphyrin which differed from the above spectroscopically, also carried a free methin group and could be converted into pyrro-aetioporphyrin by alcoholate degradation, under loss of one C-atom. The constitution of the latter compound, and of the three porphyrins mentioned, was subsequently practically completely clarified by synthetic means.

Pyrroporphyrin is a tetramethyl-diethyl-monopropionic acid-porphin. Closely related to it is rhodoporphyrin, which has a carboxyl group at the free methin group of the pyrroporphyrin.

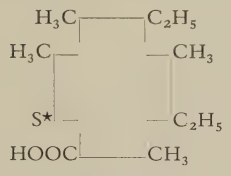
The isomer problem was particularly complicated in the case of these porphyrins, because 24 in all exist for each of the porphyrins.

The principle of constitution determination was as follows: there are 8 isomers of tetramethyl-*tri*ethyl-monopropionic acid-porphins: all 8 were synthesized. If we remove from these *tri*ethylporphins one ethyl residue, we obtained the pyrroporphyrin type, of which 24 isomers exist, because one ethyl group each can be removed from the 8 isomeric triethylporphins. By indirect means, we reintroduced the ethyl residue into the natural pyrroporphyrin, and obtain 1,3,5,8-tetramethyl-2,4,6-triethylporphin-7-propionic acid, which is derived from aetioporphyrin III. This proved the derivation of pyrroporphyrin from aetioporphyrin III, but not the position of the free methin group, which could be present in 2-, 4-, or 6-position. The 6-position was proved by synthesis of 1,3,5,8-tetramethyl-2,4-diethyl-7-propionic acid-6-carboxylic acid-porphin, which thus carries the carboxyl group at 6, and was proved to be identical with the natural rhodoporphyrin. At the same time, the synthesis

was effected of 1,3,5,8-tetramethyl-2,4-diethyl-7-propionic acid-porphin, which was found to be identical with the «natural pyrroporphyrin». This proved the 6-position of the characteristic groups of the principal chlorophyll-porphyrins and also that of phylloporphyrin, because phylloporphyrin can be converted into pyrroporphyrin with the assistance of alcoholate. Pyrro- and rhodoporphyrin therefore have the following constitutional formulae:

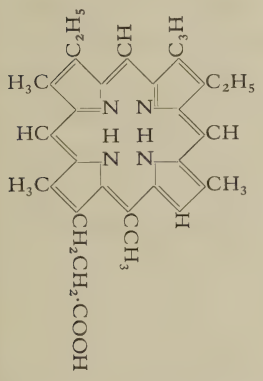


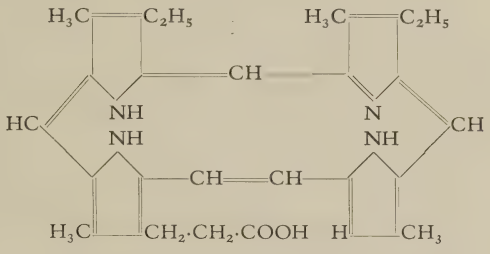
Pyrrophorphyrin



Rhodoporphyrin

Phylloporphyrin is represented by one of the following diagrams:





as was proved by synthesis; the position of the bonds, as different from the blood pigment porphyrin, has not been clearly established as yet.

What has however been established is the relative position of the substituents of rhodo-, pyrro-, and phyllo-porphyrin, which agrees in principle with those of the blood pigment, a proof which has recently been confirmed by conversion of chlorophyll-pyrroporphyrin into mesoporphyrin IX.

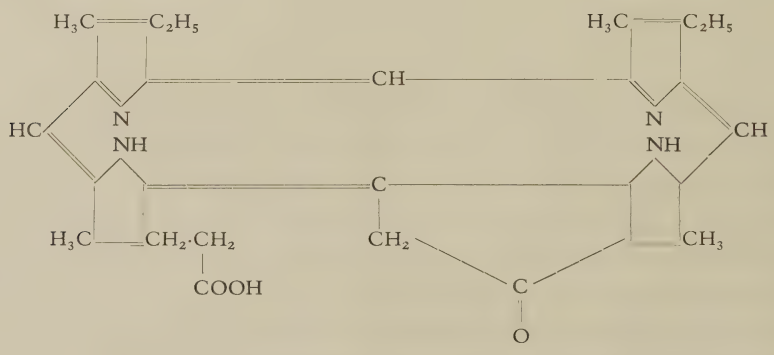
The chlorophyllporphyrins mentioned are isolated by energetic degradation with alcoholate, and the question that remained to be solved was whether chlorophyll is in fact based on the porphin nucleus.

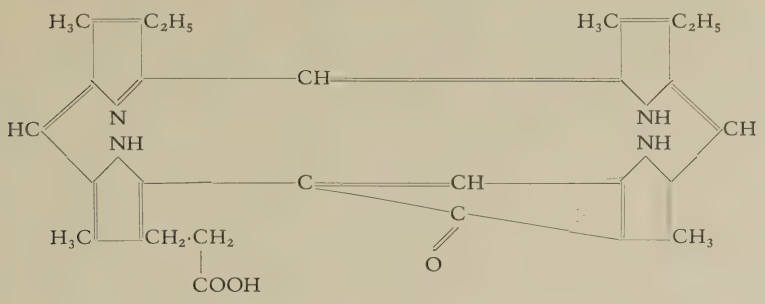
Mild degradation of chlorophyll derivatives with hydrogen iodide, formic acid, and other reagents led to numerous porphyrins, which we shall not discuss in detail.

If we consider further that the phylloerythrin isolated by Löbisch and Fischler, and also by Marchlewski, must be considered to be a porphyrin on the strength of spectroscopic analysis, and that this substance has recently been produced by purely chemical means from phaeoporphyrin a_6 and a_5 by exposure to glacial acetic acid – hydrogen bromide at 45°, there can hardly be any doubt that chlorophyll is not based on the porphin nucleus itself, but on a system closely related to it. It should be noted that substances spectroscopically analogous with chlorophyllchlorines and -rhodines are relatively easily obtained also by synthesis.

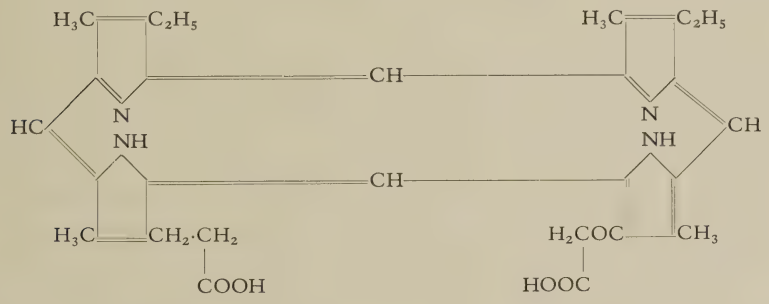
Dehydration of porphinpropionic acids leads to rhodines; reduction of porphyrins with alcoholates, in particular of iron salt, to chlorines; as does oxidation of the porphyrins with sulphuric acid and hydrogen peroxide. The chlorine spectrum can however also be produced by mere heating of the porphyrins in inert solvents, and exposure of coproporphyrin to light leads to chlorine.

Phylloerythrin is produced biologically from chlorophyll in the gastrointestinal tract of ruminants, where fermentation processes above all take place, so that we can assume at least as a working hypothesis that phylloerythrin in principle is close to chlorophyll in structure. The constitution of phylloerythrin has recently been determined with some probability, but, as in the case of phylloporphyrin, the mode of linkage of two pyrrole nuclei has not been definitely established. The following two formulae for phylloerythrin are therefore under discussion:

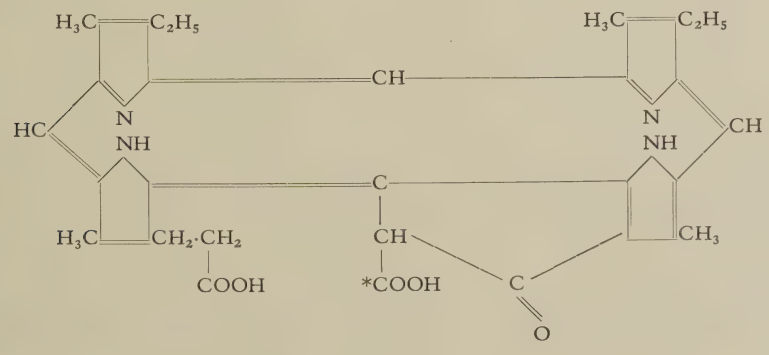




According to this, the relationships between chlorophyll and blood pigment are closer than has been assumed hitherto, if, as is most probable, the first of these formulae for phylloerythrin is the correct one, because phylloerythrin will then be relatively closely related to mesoporphyrin. If we imagine oxidation in this in the β-position at a propionic acid residue, as has been demonstrated by Knoop and others for the oxidative degradation of fatty acid, we arrive at a porphin-ketopropionic acid having the following formula:



If we assume dehydrating combination of the reactive methylene group in the keto side chain with a methin group in the α-position, we obtain the following formula:



whose close relationships to phylloerythrin are evident, and whose carboxyl group marked with an asterisk* must have the instability which characterises a carboxyl group in chlorophyll itself and in derivatives close to it. Under energetic alkali action, the carboxyl group is separated and the intermediate phylloerythrin is converted into phyllo- and rhodo-porphyrin by hydrolytic or reductive oxidative disruption of the CH_2–CO link, as has been established by experiment. Evidence of the above relationships still remains to be produced, as indeed the chlorophyll molecule still presents many riddles whose solution will present difficulties considering the instability of the molecule, in connection with which we must stress in particular the spectroscopic difference of the derivatives closest to chlorophyll and of the porphyrins. This difficulty has however largely been overcome by analytical and synthetic experiments. Mild reduction leads to porphyrins, and Nature herself brings about porphyrin formation by phylloerythrin formation in the organism of ruminants. Thus difference in constitution between the porphyrins and chlorophyll cannot be very great, as is also proved by the synthetic production of chlorines. Chlorines can be produced by reductive and by oxidative means from porphyrins; the chlorine spectrum even occurs under mere heating of the porphyrins in inert solvents, and on exposure of porphyrins to light. Numerous methods are available for porphyrin syntheses. Those close to chlorophyll must therefore also be amenable to synthesis. Further work is required on reconversion of chlorophyll porphyrins obtained analytically into chlorines, and on their biological behaviour, but an even larger number of investigations will be needed for clarifying the constitution of chlorophyll.

Since the sequence of the substituents in chlorophyll is known, the way is open on principle for systematic synthetic research, and because porphyrins occur in plants, we would seem to be justified in assuming a common evolutionary origin of the two pigments necessary for the life of animals and plants, a hypothesis which well merits experimental treatment.

Biography

Hans Fischer was born in the July 27, 1881 at Hoechst, on the river Main, in Germany. His father was Dr. Eugen Fischer, Director of the firm of Kalle & Co, Wiesbaden, and Privatdozent at the Technical High School, Stuttgart; his mother was Anna Herdegen. He went to a primary school in Stuttgart, and later to the « humanistische Gymnasium » (grammar school with emphasis on the classics) in Wiesbaden, matriculating in 1899. He read chemistry and medicine simultaneously, first at the University of Lausanne and then at Marburg. He obtained his chemistry degree under T. Zincke at Marburg in 1904; two years later, in 1906, a licence for medicine was conferred on him at Munich. In 1908 he qualified for his M.D. under F. von Müller, also at Munich.

Fischer spent his first working years at the Second Medical Clinic in Munich and at the First Berlin Chemical Institute under Emil Fischer. He returned to Munich in 1911 and qualified as lecturer on internal medicine one year later. In 1913 he was appointed E. F. Weinland's successor at the Physiological Institute (O. Frank) in Munich, where he became a lecturer on physiology. In 1916 Fischer followed the invitation of the University of Innsbruck to succeed Windaus as Professor of Medical Chemistry; from there he went to the University of Vienna in 1918.

From April 1, 1921 until his death he held the position of Professor of Organic Chemistry at the Technische Hochschule (Technical University) in Munich, as successor to Wieland.

Fischer's scientific work was mostly concerned with the investigation of the constitutive properties of the pigments in blood, bile, and also leaves, as well as with the chemistry of pyrrole. The main reason for the latter investigation was the synthesis of these natural pyrrole pigments. Of special importance was his synthesis of bilirubin. His numerous papers were mostly published in *Liebigs Annalen der Chemie* and *Hoppe-Seylers Zeitschrift für physiologische Chemie*.

In recognition of his work in these fields, the title of « Geheimer Regierungsrat » (Privy Councillor) was conferred upon Hans Fischer in 1925; in 1929 he

was awarded the Liebig Memorial Medal; Harvard University bestowed the title of honorary doctor on him in 1936; he received the Davy Medal in 1937. Fischer received the greatest honour of all, the Nobel Prize for 1930, for his work on the chemistry of pyrrole and the synthesis of haemin. In 1935, Professor Fischer married Wiltrud Haufe.

He died on March 31, 1945 in Munich.

Chemistry 1931

CARL BOSCH

FRIEDRICH BERGIUS

« in recognition of their contributions to the invention and development of chemical high pressure methods »

Chemistry 1931

Presentation Speech by Professor W. Palmær, member of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

Under Alfred Nobel's will, the Nobel Prizes are to be awarded to those who have been of the greatest benefit to mankind and, particularly in respect of the Prize for Chemistry, it is stipulated that this shall go to the person who has made the most important discovery or improvement in chemistry. Although, by reason of their brevity, the few lines by which the great donor indicated the purpose of the Prizes have given rise to certain difficulties in interpretation and conversion into reality, yet it would seem that there has never been any doubt, nor can there be, that it is first and foremost the benefit to mankind which governs the bestowal of the Prizes.

This is not contradicted by the fact that the Nobel Prizes for Chemistry have hitherto been awarded exclusively for scientific work. For quite apart from the fact that on some occasions the importance of the work involved « to the development of the chemical industry » is given expressly in the brief words which in the Diploma state the service which is being rewarded by the Prize, in the majority of cases the benefit which these works provide is already manifestly clear and in many cases they have also led to practical application of the greatest possible value.

If, therefore, works which were aimed directly at the achievement of technical improvement and practical progress have not hitherto been rewarded by bestowal of the Nobel Prize for Chemistry, then a contributory factor has been that technical progress has frequently been the outcome of co-operation among several people, and that it is not always easy to decide which of them is the most deserving.

This year, however, the Academy of Sciences believes it has discovered a technical advance of extraordinary importance and in respect of which it is also quite clear to which persons the principal merit is to be ascribed.

The Academy has therefore decided to divide this year's Nobel Prize for Chemistry equally between Professor Carl Bosch and General Director Friedrich Bergius, by reason of their services in originating and developing chemical high-pressure methods, and I will now endeavour to describe in a few

words the significance of these services – a task which comes easy in so far as their importance to humanity is obvious.

Everyone knows what happens when a bottle of carbonated water is opened: there is a « pop », and a gas, carbon dioxide, rushes out. This gas also emerges from the whole liquid in bubbles. When the water was prepared the carbon dioxide was forced into the water under pressure, and, with increasing pressure, more and more carbon dioxide can be forced into the water in a dissolved state. If, then, the pressure is reduced, a corresponding quantity of carbon dioxide escapes. Furthermore, when the carbon dioxide is absorbed into the water, a chemical change takes place, a part of the gas combining with the water to form what is known as carbonic acid hydrate, a chemical compound which, at low pressures, only forms in small quantities but, at high pressure, does so in ever increasing quantities. If the carbon dioxide gas is compelled, by the exertion of pressure, to dissolve more and more in the water then, by reason of the apparent disappearance of the carbon dioxide gas, a reduction in volume occurs.

According to the laws of chemical equilibrium it is generally true that if reduction in volume occurs during a chemical change in which gases are involved and if that change is due to the fact that the quantity of the gas or, in scientific language and more accurately expressed, the number of gas molecules is less after the change than prior to it, then the change, i.e. the yield of the product striven for, is promoted by the fact that pressure is exerted on the mixture of the various substances in which the change occurs. This can also be expressed by saying that the mixture yields to the pressure, i.e. by the disappearance of gaseous substances. This has long been known, but only of late has this law been industrially exploited, humanity thereby deriving a high degree of useful and important benefit from the process.

When Haber, in 1908, approached Germany's then largest concern in the field of the chemical industry, namely the *Badische Anilin- und Sodafabrik A.G.*, in order to try to interest them in producing ammonia by the direct combination of its components, the gases nitrogen and hydrogen, he was able to point out that he had succeeded in finding two substances, namely osmium and uranium, which acted as powerful contact substances or catalysts, – i.e., their presence accelerated the change which apparently otherwise would not occur, to such an extent that, with the help of pressure, a practical exploitation of the fact was now conceivable as a means of producing ammonia, from which, by absorption of the latter into sulphuric acid, unlimited quantities of that excel-

lent nitrogenous fertilizer, ammonium sulphate, could be produced from the nitrogen in the air. In this case, in fact, pressure promotes the change to a very great extent, because the volume of the mixture of nitrogen gas and hydrogen gas from which the ammonia is made, is here compressed to half. By taking this step, Haber had given rise to a new method of utilizing the nitrogen in the air, for which he has already been rewarded by the Nobel Prize for Chemistry.

Nevertheless, it was still a tremendous step from providing the scientific basis of ammonia synthesis, as the production of ammonia by combining its component elements nitrogen and hydrogen is also termed, to its realization on an industrial, i.e. economically successful scale. This task was entrusted by the « B.A.S.F. », as the firm mentioned above is generally called, to Dr. Carl Bosch. It soon became clear that, in order to achieve a rate of transformation and a yield satisfactory under practical conditions, it was necessary to work at a pressure of approx. 200 atmospheres and a temperature of around 500° C. In experiments to carry out the chemical process under these conditions, however, Bosch encountered one difficulty which appeared at the outset to be insuperable. This was the fact that it appeared impossible to find a material which, at the pressure and the temperature mentioned, would stand up to the mixture of gas involved for any appreciable time. For example, steel was attacked by hydrogen and thus lost its resistance to pressure.

Then Bosch had the brilliant idea of overcoming these problems in the following way. The apparatus in which the change takes place was to have double walls and comprise an inner cylindrical tube enclosed by another outer tube, so that a space was left between the two tubes. The reaction was to take place in the inner tube at 200 atmospheres pressure and 500° C – a temperature which would be maintained by the heat generated during the reaction. The cold, compressed mixture of hydrogen gas and nitrogen gas would be introduced into the space between the two tubes so that the space would be kept relatively cool, while the pressure, on the other hand, would be as high as in the interior tube. In this way, the material of which the inner tube was composed would have only to withstand the high temperature without at the same time being exposed to any pressure stress, whereas the outer tube would only have to withstand a pressure stress at a relatively low temperature.

In order to carry this really inventive and brilliant idea into effect, it was essential to find material to satisfy both purposes. As regards the outer tube, this presented no real problems, because ordinary carbon steel will withstand 200 atmospheres pressure at a moderate temperature. With regard to the material for the inner tube, careful and systematic investigation showed that,

inter alia, low-carbon chrome steel containing a small percentage of chrome met the requirement.

On this basis, it was possible, just before the outbreak of the World War, to introduce the first high-pressure method into the chemical industry. Naturally, for economic exploitation of the chemical transformation, research was necessary in other respects – indeed, in this special case, particularly as regards the production of cheap hydrogen gas and as regards the contact substances, since those discovered by Haber were not suitable for practical operation – but since the work in connection therewith is not the object of this Prize, it is superfluous to deal with this aspect in greater detail.

On the other hand, it would be as well to recall the enormous importance of this first high-pressure method. It has been shown that ammonia synthesis is not only more generally applicable than the conventional methods of converting the nitrogen contained in the air into fertilizer, i.e. the manufacture of calcium nitrate or crude calcium cyanamide, but is also now economically more advantageous in almost all countries. At present, it has been introduced in 14 different countries. The danger which threatened mankind – that stocks of Chile saltpetre (sodium nitrate) (hitherto the most important nitrogen-bearing fertilizer) would be exhausted in the not-too-distant future – has been removed by the methods which are now under discussion. But this is still not enough. Whereas it was considered a tremendous success in the past that the nitrogen fertilizer obtained from the nitrogen in the air, e.g. in the form of calcium cyanamide could be sold at the same price as Chile saltpetre, ready-made by Nature, the synthetic manufacture of ammonia or ammonium sulphate has in recent years resulted in an actual reduction of the previous, certainly somewhat artificial price of Chile saltpetre.

Now that the first high-pressure method has been introduced into industry with the greatest possible success, Bosch, as technical director of the giant German chemical industrial concern *Interessen-Gemeinschaft Farbenindustrie Aktiengesellschaft*, which, for brevity is generally referred to as «I.G.», has also introduced other high-pressure methods. These come in the field termed «carbon raffination», and in the main set out to obtain organic compounds of hydrogen and carbon monoxide. The greatest success was the «brilliant synthesis» – in the words of an authority and a proposer – of methyl alcohol or methanol – known in its impure state by the infamous name wood alcohol – from the substances mentioned. In recent years, production of this important substance, which forms the starting material for manufacture of the well-known disinfectant formalin, has been undertaken on the largest scale

by this method, and not only in Germany but also, for example, in the United States of America, which has meant a drop in the price of the product. It is, of course, facts of this nature and hardly any others which, in the final analysis, prove the merits of any technical work. Quite a number of other valuable organic compounds can also be obtained from hydrogen and carbon monoxide by varying the pressure, temperature, and contact substances, so that it seems justified to assume that the manufacture of further such substances by the method discussed will be industrially exploited.

A few years after Bosch had started the work which was to lead to the first industrial chemical high-pressure method, Dr Friedrich Bergius, independently of B. A. S. F., instituted investigations and work which was also to motivate his using the high-pressure method.

The purpose of this work was to resolve a problem which, in importance, can be compared with the nitrogen problem, namely the manufacture of oils and liquid fuels from solid coal, such as pit coal and brown coal (lignite) – which is also known as liquefaction of coal. The products mentioned, which consist, in various proportions, of carbon and hydrogen and which are therefore referred to as hydrocarbons, were considered necessary to modern living, with vehicles and ships being run on petrol and other liquid fuels. Since the natural stocks of petroleum are fairly restricted, we would sooner or later be faced with the need to restrict the use of oil for the purpose mentioned or even to stop using it altogether, unless methods were available whereby these oil products could be artificially made from other crude materials at an acceptable price.

If we consider the earth as a whole, then the raw material *par excellence* is pit coal. However, this is not by any means pure carbon, but also contains hydrogen and oxygen. When various types of coal are heated in retorts or generally enclosed vessels from which air is excluded – so-called dry distillation – coke remains, while the hydrogen is released, partly as volatile hydrocarbons and other chemical compounds and partly in a free state or as worthless water. Apart from the gas which is obtained in this way – illuminating gas, or cooking gas – we obtain hydrocarbon-bearing oils and tar, though in relatively small quantities. The biggest part of the coal is left as coke, and a considerable part of the carbon and hydrogen is released in the form of gaseous substances.

Therefore, it is not unjustified if we consider destructive the simple carbon distillation, which has been carried on for some hundred years or so, if the

purpose is the manufacture of oils, because a good part of the hydrogen escapes without being bonded to the carbon, although the former still has value as a gaseous fuel and, what is more, some of the hydrogen is directly lost in the form of water.

The fundamental idea in the process conceived by Bergius, and also known as Berginization, is the following. Simple distillation of coal can, so to speak, be carried out with varying degrees of violence, i.e. at higher or lower temperatures. In the first case, the oil yield is poorer and in the second better. To start with, Bergius set out to carry out distillation gently so that, properly speaking, the greatest possible quantity of oil would be yielded. However, this had also been done by others. Furthermore, though, Bergius – and this is the essential feature in his inventions – wanted at the same time, while the distillation was taking place, to force in hydrogen under high pressure, resulting in more hydrogen combining chemically with the coal, so that a considerably larger quantity of the carbon contained in the coal is transformed into oils than is possible with conventional distillation of coal. In other words, the basic idea is that the valuable solid hydrocarbon compounds which occur in pit coal are not just destroyed by excessive heating or partial combustion, but are safeguarded and, furthermore, are converted into liquid oils by the injection of hydrogen under pressure. Bergius, too, therefore, came to realize that a high-pressure method had to be employed, and developed independently to quite a considerable degree the technique of working with high pressure.

There is however another circumstance of considerable importance to the achievement of a satisfactory result. In the destructive, simple distillation of coal, heat is generated. Furthermore, as already mentioned, the oil yield is poorer at high temperatures. On the other hand, where coal is heated, by itself, in hydrogen gas and under high pressure, undesirable localized overheating occurs, resulting in increased coking and gasification with reduced formation of oil. In order to achieve a more even heat distribution and exact regulation of temperature, Bergius had the idea of suspending pulverized coal in oil and treating this mixture with hydrogen gas under high pressure. In this way, the heat generated is satisfactorily distributed, and localized overheating avoided. By this same means, he also obtained the extremely important advantage that the coal to be processed could be pumped together with the oil into the reaction apparatus, thus permitting continuous operation. These two features must be regarded as important inventions.

For production under factory conditions, an exactly regulated temperature (usually 400 to 500° C) is applied, with a pressure of 100 to 200 atm.

According to the composition of the coal, it is possible in this way to extract 50 to 70% of the carbon contained in the raw material in the form of oils, of which benzine represents about one-third, the remainder comprising diesel oil, fuel oil, and asphalt, together with carbolic acid and other phenols.

At the outset, Bergius worked without catalysts. Since the commencement of collaboration between him and I.G. – or « Industrial Giant » as these letters have come to be interpreted in America – catalysts have been used. This collaboration with I.G., who were able to make available their tremendous experience in the field of high-pressure technique and contact substances, certainly promoted the extremely important development which the liquefaction of coal by Bergius' methods then underwent. In the giant Leuna plant founded in 1926, near Merseburg in Saxony, the year 1930 saw the production of no less than 250,000 tons of *benzine* from brown coal, of the carbon content of which no less than 80% was utilized in the form of oils. In Germany, a large plant was also set up for processing the residues of oil distillation and tar oils. Steps have also been taken towards co-operation with the oil syndicates in America, where the high-pressure method is applied to a considerable degree, especially in order to convert not readily volatile hydrocarbons or crude oil into far more valuable *benzine*. The ease with which the hydrogen treatment under pressure can be adapted to the various problems of the petroleum industry is obviously of the utmost importance. As far as our country is concerned, the possibility of obtaining oils from timber by high-pressure processing is of particular importance.

In other words, two problems of the utmost significance to humanity have been resolved by the chemical high-pressure methods – one during recent years, the other somewhat earlier. The difficulties – we might say enormous difficulties – and significant risks which proved obstacles at the start have been overcome, and the methods are now to a great extent danger-free and operationally reliable. This is why, in recent times, they have also been used for the manufacture of products other than those mentioned. However, it does not seem necessary to dwell further on this aspect. It ought in any event to be obvious that the introduction of the chemical high-pressure methods represented an epoch-making improvement in the field of chemical technology, and that no other improvement in the same field in recent times can measure up to it, so that the award of the Nobel Prize would seem to be outstandingly justified.

Professor Bosch. The Royal Academy of Sciences has decided to reward with this year's Nobel Prize for Chemistry services in connection with the origin and development of the chemical high-pressure methods and to divide the Prize between two persons who, in the Academy's view, have above all others merited this distinction.

You, Professor Bosch, were the first to enrich the chemical industry with this powerful tool, for the production of ammonia from the elements. Between the presentation of the scientific bases of this synthesis and its industrial exploitation lay a mighty chasm, which you bridged, *inter alia*, by the brilliant invention and construction of the high-pressure apparatus. By doing so, you made it possible for nitrogen to be made available to mankind in inexhaustible quantities, in a form suitable for agriculture, and even at lower prices than hitherto. Furthermore, you developed high-pressure methods for the production of other important substances. By virtue of this, the Academy wishes to thank you and congratulate you, and requests you to receive the distinction from the hands of His Majesty the King.

General Director Bergius. You undertook to tackle a problem which, in its importance for humanity, can be compared with the solution of the nitrogen question. You have shown how, by the injection of hydrogen under pressure, pit coal, brown coal, and other carbon-bearing materials can be processed to liquid fuels which are considered indispensable in modern life for the propulsion of ships and vehicles. You have thereby obviated the danger which threatened of exhaustion of petroleum deposits, an event which must have happened sooner or later. In your work, you arrived at the high-pressure method quite independently. On the basis of your work, a powerful industry has already been formed.

I have the honour to extend to you the Academy's thanks for these services and to congratulate you on the distinction which you are now about to receive.

Carl Bosch

The development of the chemical high pressure method during the establishment of the new ammonia industry

Nobel Lecture, May 21, 1932

The eminent distinction of the Nobel Prize award which imposes on me the pleasant duty of delivering a lecture to you to-day is in recognition of the development of the high pressure techniques, i.e. the methods used to perform chemical reactions at elevated temperature under pressures of 100 atmospheres and higher.

The technical development of these processes within the I.G. Farbenindustrie concern, a task with which I have been entrusted for about 25 years, posed a profusion of scientific, technical and economic problems the solution of which occupied hundreds of scientists and which affords a living to many thousands of people.

I can only report here on a small section of our sphere of work and with an eye to the motives underlying the award of the prize I have chosen to discuss the solution to the question of apparatus.

Partly as a result of the Lecture given by Haber here in Stockholm in 1920 it has been learned that in 1908 he approached the Badische Anilin- und Sodafabrik with the suggestion to attempt the technical synthesis of ammonia from hydrogen and nitrogen under high pressure. In the course of his studies on the position of the equilibrium in the system ammonia $\rightleftarrows$ hydrogen + nitrogen he ascertained that the foreseeable shifts in equilibrium for high pressures actually occur in favour of the ammonia, but – and this was a particularly encouraging and for us decisive fact – he also found that osmium and uranium markedly accelerated the attainment of the equilibrium and brought it about at a far lower temperature than the catalysts exclusively used hitherto, i.e. manganese, iron, platinum, etc.

When the management at the time entrusted me with the task of expanding the conversion of this high pressure synthesis to an industrial scale with a view to its economic application, it was obvious that there were three main problems which had necessarily to be settled before the construction of a

plant could be undertaken. These were: supply of raw materials, i.e. of the gases hydrogen and nitrogen, at a lower price than hitherto possible, the manufacture of effective and stable catalysts, and lastly the construction of the apparatus. These problems were dealt with simultaneously.

To begin with, sufficient pure hydrogen for the tests was available from chlorine electrolysis and yielded the required nitrogen-hydrogen mixture by combustion with air. None of the then known hydrogen processes was suitable for large-scale manufacture. We examined all of them but without exception they were too expensive or yielded insufficiently pure gases. It must not be forgotten that the procurement of hydrogen is the largest item in the prime cost, at least nowadays since because of the efficiency of the high pressure synthesis the conversion of the ready-made gas mixture into ammonia is only a minor cost factor. Since we were dependent on coal as a starting material we at once decided on the sole eligible source in our situation, water gas from which nowadays, after a short transition period – separation of the hydrogen by Linde's low temperature liquefaction method – hydrogen is manufactured in enormous quantities by a *catalytic* process developed by us.[1]

The accomplishment of the second task was no less significant. Osmium, a very good catalyst, was difficult to maintain since when in its active, i.e. finely disperse, form it comes into contact with air (never wholly avoidable under industrial conditions) it readily volatilizes as osmium tetroxide, but in particular because the whole world's supply amounted to only a few kilograms, hence at best we could have based only a very moderate manufacture on osmium. Uranium was expensive, of course, yet nevertheless obtainable in some quantity but proved extremely sensitive to oxygen and water and it could not, and still cannot, be converted by any means into a form that can be used for a mass-production process. However, as a result of very broadly based series of experiments using our rapidly expanded experimental technique, we succeeded in preparing relatively fast-acting, technically perfect, easily manipulable, stable and inexpensive catalysts, chiefly those with iron as the active substance* which are currently in universal use presumably exclusively for the synthesis of ammonia. They are a completely new type of catalyst, their characteristic being that they no longer consist of pure elements in varyingly fine form, but are mixtures.[2] It was only after studies extending over many years and also only in the light of recent theoretical knowledge

* Molybdenum, particularly in mixtures, was also found to be an excellent catalyst; D.R.P. 246, 377, October 22, 1910.

that we were able to clarify the specific action of these mixed catalysts, although at the very outset we had formed empirically a broadly correct idea which assisted us not a little in our studies.*

The successful conclusion of the third task, which is the only one I intend to discuss to-day in more detail, related to the apparatus. There were no examples in industry. The only technique, and that of a physical nature, involving high pressures, was Linde's liquefaction of air. The conventional apparatus for this was made from soft soldered copper and was hence unsuitable for temperatures up to 600° C and locally still higher. In true awareness that the manufacture of the apparatus would be one of the most difficult tasks, quite apart from surprises yet to come and soon forthcoming, an immediate start (a typical feature of our work) was made on fitting up a workshop specially adapted to our needs which first had to make the apparatus necessary for the laboratory work. Right from the start this test apparatus was of very serviceable design since the individual tests all took a very long time as it was particularly important to ascertain the stability of the new catalysts in experiments of long duration. We took as our starting point the apparatus used by Haber for his tests and of which I append an illustration (Fig. 1). The contact mass, surrounded by tightly packed insulation, is in the centre of the steel vessel which is cooled with ice water. The gas lead, heating arrangement and temperature measuring device are plainly shown in the figure. As this apparatus suffered from many drawbacks for prolonged experiments, it was completely redesigned and finally in this form (Fig. 2) 24 of them were in continuous day and night service for years.

With its aid we were able to conduct the many separate examinations necessary for the discovery of the catalysts and for development to maximum efficiency, which over the years grew to the number of 20,000. With a small model of this sort there are no special difficulties since air cooling ensures the stability of the outer pressure-bearing parts and of course the mechanical stress on the inner parts is only slight.

The state of affairs was soon to change when we started to build a smaller convertor as a production apparatus. Haber had already attempted something

* «The outstandingly potent action of catalysts made in that way... is presumably attributable to the fact that the admixtures referred to dissolve or become finely disperse in the highly heated metal oxide, whereby during the subsequent reduction an otherwise scarcely perceptible skeleton forms within the metal mass and inhibits extremely effectively any deterioration of the surface and hence of the catalytic properties». (Extract from D.R.P., 254, 437, April 22, 1910.)

along those lines on a very small scale but had only run it for one or two hours when it failed for design reasons.

We therefore then built an apparatus of which the chief, and for us the most important and interesting part, except for a circulation pump and the ammonia separator, was a contact tube of the shape and size illustrated in Fig. 3 (wall thickness about 30 mm). This tube was heated on the outside. Being cautious we had housed it in a strong, reinforced concrete chamber far away from all the busy centres of activity since in the meantime we had also become familiar with the danger of fires and flarebacks which occur, frequently with spontaneous ignition, when hydrogen emerges at high pressure.

The two tubes drawn by Mannesmann had each done service for 80 hours, then they burst. If we had charged them with osmium instead of with our new catalyst, the world's supply of this rare metal which we had already bought up would have disappeared.

It was found on examination of the burst tubes that they were swollen and it was apparent that owing to some change of the material the inner wall had altogether lost its elasticity and the change had continued until finally the undamaged part became too thin and yielded to the internal pressure. This is illustrated in Fig. 4A. A chemical attack was the first thought. But what could have happened? To begin with, hydrogen seemed harmless, nitrogen being more suspect since, according to the available literature, iron nitride was apt to form and was described as a silvery, brittle compound forming readily from ammonia and iron. Chemical analysis showed no trace of nitrogen in the embrittled material. More detailed information was obtained by metallographic analysis, a test procedure then almost unknown in chemical engineering and with which I was acquainted only because I had begun my career as a metallurgist. The following picture emerged:

Carbon steel, the only suitable type owing to its mechanical strength, has a structure in which carbonaceous perlite is dispersed in a matrix of pure iron (ferrite). In the changed inside of the used tubes the perlite had disappeared and the structure had been destroyed by cracking. Decarburization of the iron had thus occurred and pure, soft iron should have been formed. But that was obviously not the case as the changed material was hard and brittle. Hydrogen was in fact found to have penetrated the iron and formed a brittle alloy, in the same way as carbon forms brittle iron carbide with iron.*

* As subsequent examinations showed the cracking is essentially caused by the decarburization of the perlite with the formation of methane which becomes enclosed in the structure under extremely high pressure and, together with the mechanical stress on the material, loosens the structure.

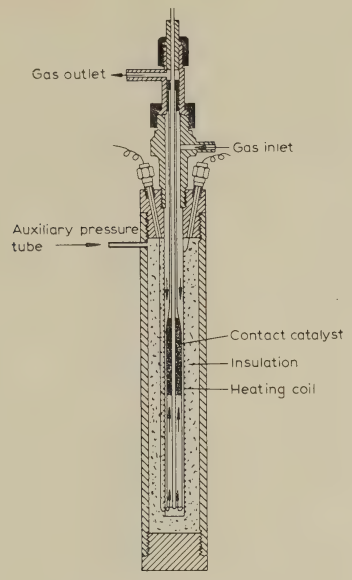


Fig. 1. Haber's experimental convertor, 1909.

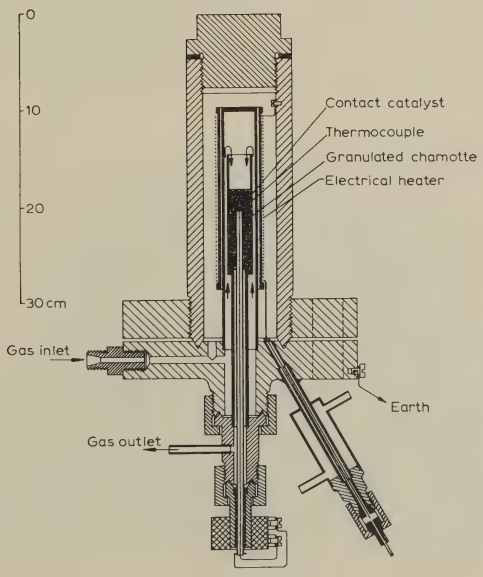


Fig. 2. Laboratory convertor, 1910.

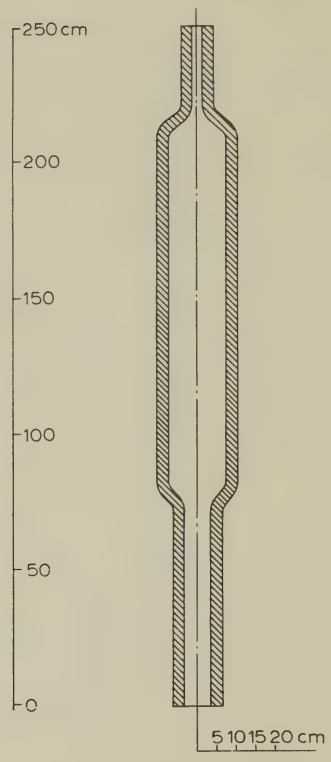


Fig. 3. Contact tube as used in first technical trial, 1910.

Fig. 4. Unprotected convertor tube, 1910.

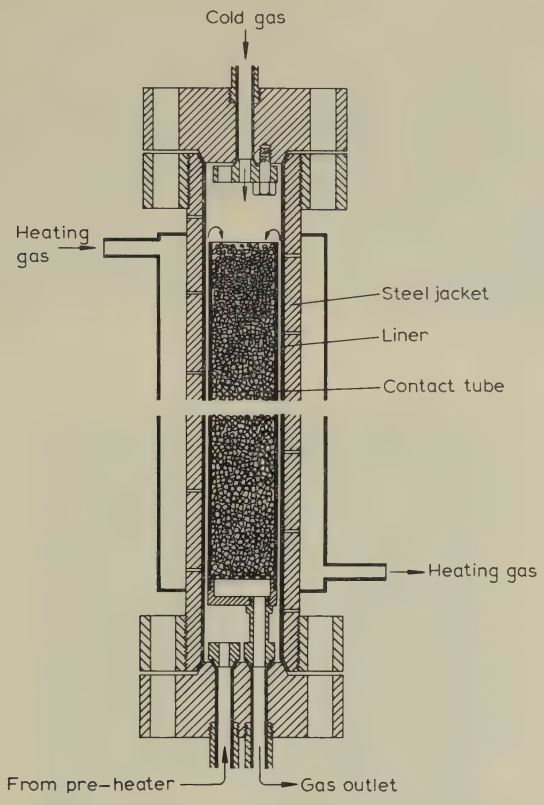


Fig. 5. First convertor with liner and external heating, 1911.

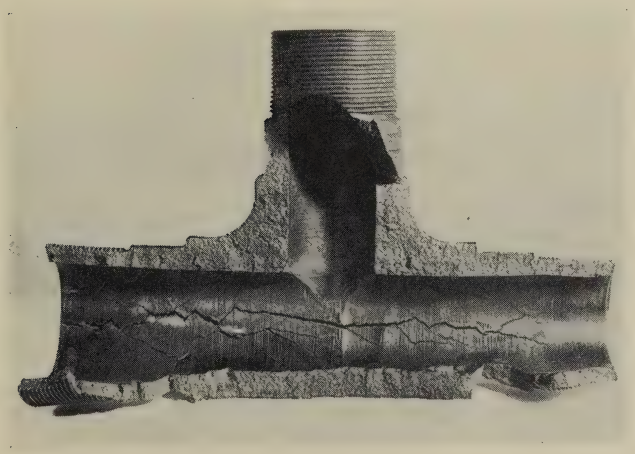


Fig. 6. Brittle fracture of a fitting owing to hydrogen attack, 1930.

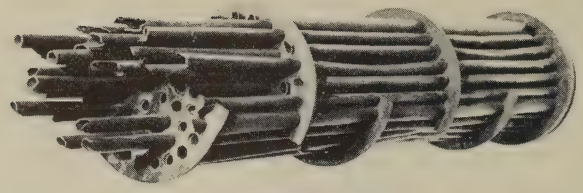


Fig. 7. Destroyed tube cluster from a heat exchanger, 1910.

Fig. 8. Hydrogen attack on a mild steel forging. General view, 1930.

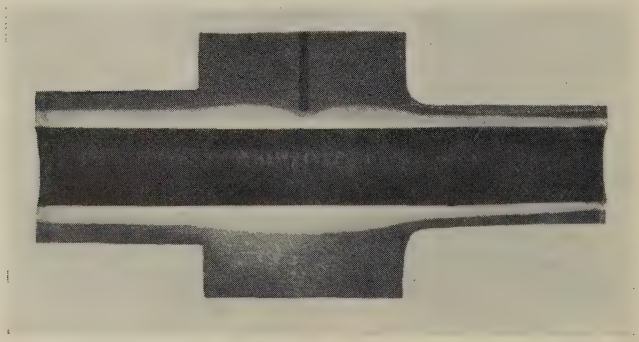


Fig. 9. Effect of wall thickness on decarburization, 1913.

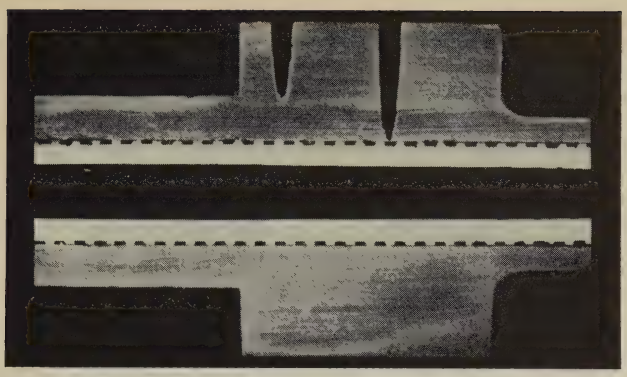


Fig. 10. Protection against hydrogen attack by liner and degasification channels, 1913.

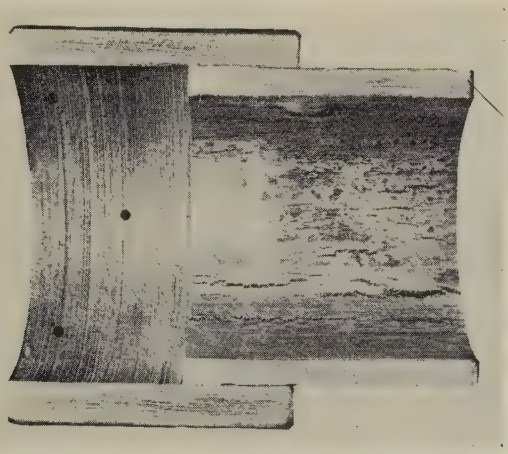


Fig. 11. Steel jacket with liner, 1911.

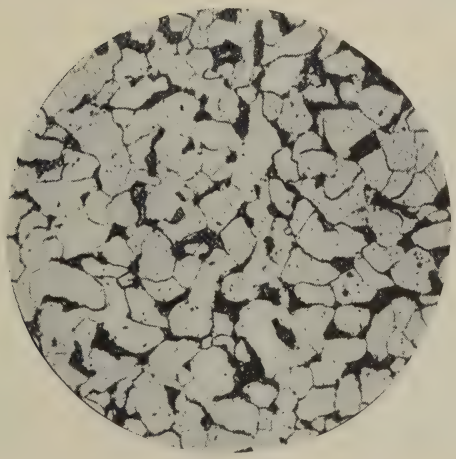


Fig. 12. Fine structure of undestroyed mild steel (× 36).

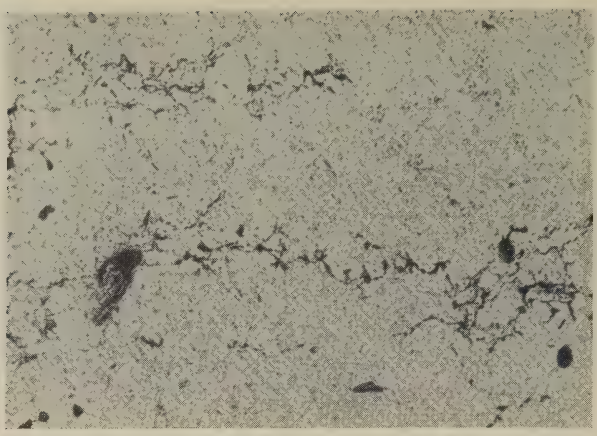


Fig. 13. Unprotected convertor tube. Fine structure of destroyed interior, 1910.

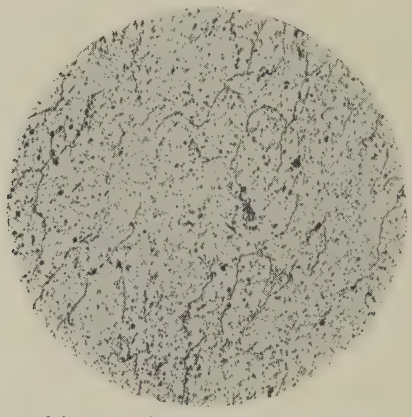


Fig. 14. Fine structure of destroyed 4.8×6 mm steel tube from a heat exchanger, 1910 (× 50).

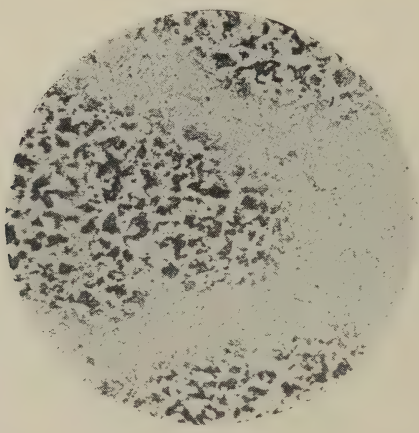


Fig. 15. Hydrogen attack on a mild steel forging. Fine structure in a ramified crack, 1930 (× 25).

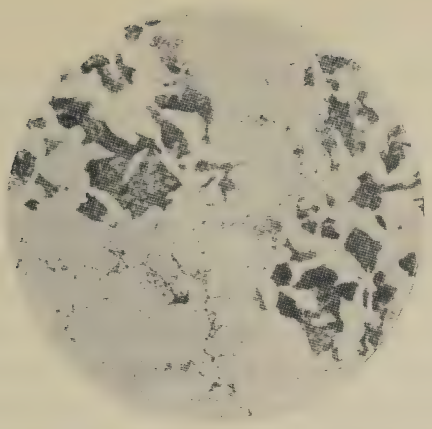


Fig. 16. Hydrogen attack on a mild steel forging. Breakdown of perlite by decarburization, 1930 (× 50).

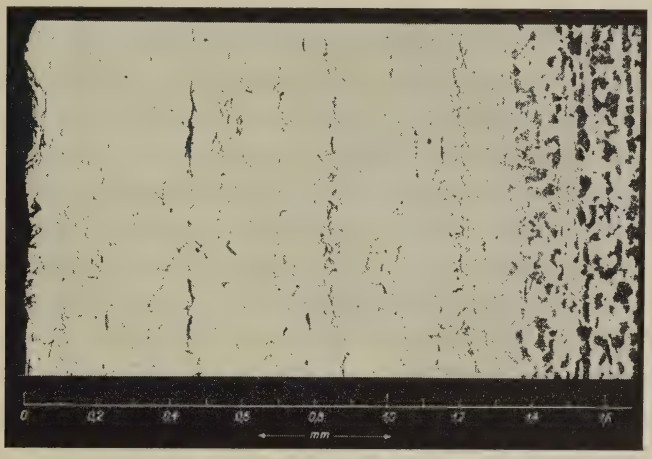


Fig. 17. Effect of hydrogen on structure of mild steel.

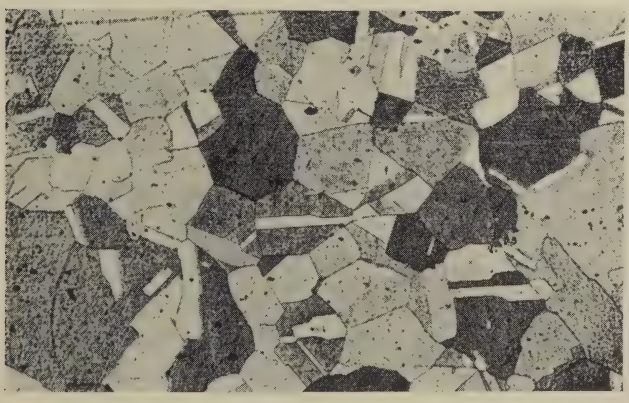


Fig. 18. Technical copper (× 40).

We were then in a dilemma. A number of attempts to obviate the difficulties which had arisen were in the first instance unsuccessful or else unpromising. Even when overheating was most painstakingly avoided the same phenomena appeared, albeit after a longer period. Tests of materials in the laboratory revealed that at high pressure and quite high temperature, carbon steel is invariably corroded by hydrogen in the manner outlined. It is just a question of time. In our case at any rate, since the best catalysts then used by us required working temperatures of not less than 400–450°C, it was only a matter of hours and days. To dispense with external heating and use stronger internal insulation with cooling on the outside and heating on the inside seemed ineffective and uneconomical, particularly since it transpired that with hydrogen under high pressure all insulations failed – and the good insulations at that – the effect of which is based on their porosity since of course compressed hydrogen has a very high thermal conductivity. Furthermore a systematic study was undertaken of all suitable metals and materials with which it would be possible to protect the steel available to us for pressure-bearing construction material. But these again were either destroyed or permitted very ready trans-diffusion of hydrogen so that no protection was achieved. Only refined steels, as we found in subsequent studies, gave better results so that they were a suitable building material and are still in use to-day.[3]

Meanwhile we had found a better and quite general solution to the problem of making apparatus with unlimited stability to hydrogen at high temperature under all conditions.

We assumed to start with that the diffusion of hydrogen into the iron, the decarburization of the perlite, and the formation of brittle iron hydride are just unavoidable. They had to be rendered harmless by a modification in design. The wall of the convertor serves two purposes: it holds the pressure of the highly compressed gases, and provides a gas-tight seal. What would be the result of separating these two functions and allocating them to different components? It soon proved practicable to do this. The very first test convertor built on this principle validated this reasoning.

The long-sought solution consisted in fitting a pressure-bearing steel jacket internally with a quite thin lining of soft steel in such a way that as the hydrogen, which of course only diffuses, passes through the thin lining it is able to escape without building up pressure before it can attack the outer steel jacket at the high temperature. This is readily achieved by the grooves produced on the outside when the tube is being turned, and by a large number of holes drilled in the steel jacket through which the hydrogen is free

to emerge. Right at the outset the thin lining tube fits tightly against the jacket under the high pressure and later, when it has become brittle, there is no way of expanding it again so that no cracks occur. Diffusion losses are minimal.[4]

The solution appeared simple and was in fact so but yet the entire development of the process depended on it to a greater or lesser extent. To-day, after 20 years' experience we know that hydrogen still attacks unprotected iron at temperatures even below 300° C and sooner or later causes breakdowns at points where frequently they would not have been expected.

I shall now demonstrate the design for you using lantern slides and then illustrate the destroying action of hydrogen using particularly explicit examples:

Our first convertor dating from March, 1911 with lining tube, still heated on the outside (Fig. 5). The regenerator is located outside the convertor.

Now examples of typical breakdowns: the extensive splintering of the material is immediately noticeable (Fig. 6). The tubes (6 mm outside diameter) had become so very brittle that they shattered on withdrawal of the cluster (Fig. 7). In Fig. 8 the zone destroyed by the hydrogen is shown in white. The finely ramified paths of attack advancing in the material as extremely fine hairline cracks are noteworthy. The next photograph (Fig. 9) shows the etched cross-section of a hollow test rod of carbon steel with a uniform inner cavity and different wall thicknesses. At the top of the thick collar a fine perforation is visible which was drilled through $\frac{4}{5}$ of the wall thickness. The decarburized zone of the material shows up light against the dark intact zone. The extent of the decarburization depends on the existing temperature, the partial pressure (diffusion pressure) of the hydrogen active in the structure and on the magnitude of the mechanical stress.

As measured in absolute terms therefore the decarburization has penetrated further in the thick wall, while measured in relative terms it has penetrated further in the thin wall. Owing to the low local diffusion pressure the corrosion recedes at the cavity.

Fig. 10 shows how the hydrogen attack is rendered harmless by lining tube and gas exhaust channels. Removal of the gas has made it impossible for the hydrogen completely to destroy the lining tube or even attack the jacket. Apart from numerous cracks the lining tube (Fig. 11) also exhibits blistering caused by the formation of methane and steam owing to diffusing hydrogen. The steel jacket itself shows no cracking at all but has widened owing to thermal expansion. Microscopic examination of the fine structure affords the best

insight into the destruction. Firstly, in Fig. 12 the fine structure of an intact ingot steel can be seen. The matrix of pure iron (ferrite) is light, the dispersed carbon-containing crystals (perlite) are dark.

A number of photographs then follow which show the destruction of the structure, a very instructive example being Fig. 13. The material is completely decarburized and loosened at the grain boundaries.

In Fig. 14 the material is also completely decarburized and loosened at the grain boundaries. Oxides are embedded everywhere in the structure.

Fig. 15 shows the fine structure of a ramification of the attacked forging in Fig. 8.

Similarly Fig. 16 which brings out particularly clearly the incipient dissolution of the perlite near grain-boundary breakdowns.

The same progression of the effect induced by the hydrogen appears in Fig. 17.

The two following photographs show copper which was tested as material for the jacket and lining, proving inferior to iron. First copper with a normal structure (Fig. 18) and then Fig. 19 showing the structure after brief exposure to the action of hydrogen at high pressure and temperature. After 40 hours the destruction had become so far advanced that the copper, in this case from a regenerator coil, was completely permeable to gas. Besides hydrogen attack on the structure there is a further factor which frequently causes breakdowns, i.e. severe cavitation within the metal (Fig. 20). The hydrogen which has diffused into the material, the methane formed by decarburization and any steam formed by the reduction of oxides are present under high pressure in the structure of the steel.

When the pressure of the ambient gas atmosphere is rapidly released the material readily expands, particularly at higher temperature at sites with small coherence beforehand such as incompletely welded blow holes and pipes or sites where there are large accumulations of slag.

I have already stated that in what are termed refined steels we found a suitable material which finds particular application at points in apparatus which are awkward to protect by a lining. Fig. 21 follows for comparison with iron (ingot steel). Refined steels are merely carbon-containing iron alloys, e.g. with Cr, W, and Ni.

Examination showed that perlite nickel steel is very sensitive to hydrogen attack, in many cases more sensitive even than ordinary ingot steel. The sensitivity rises with increasing nickel content. This influence of nickel can be offset by the appropriate addition of alloying metals such as chromium, tung-

sten, molybdenum, etc. The graph (Fig. 22) shows that for instance a tungsten content of 2% is insufficient compensation and that the loss of strength and expansion increases strongly with the nickel content. A 5% tungsten addition is adequately effective.

Next comes a figure to illustrate the effect of degasification (Fig. 23). It can clearly be seen that the destruction stops short a certain distance from the degasification channels and that the jacket tube is not attacked. In the present instance the jacket and lining tubes are of different materials (jacket tube of ingot steel, lining tube of ingot iron).

A further means to inhibit the attack of hydrogen on the iron is to flush the space between the lining tube and the jacket continuously with nitrogen.[5] As I have previously mentioned nitrogen is not harmful to iron. The effect of this arrangement is exactly like that of gas exhaustion, as shown in Fig. 24. The method is applied on a wide scale in conjunction with gas exhaustion.

Elsewhere[6] it was found that instead of the neutral gas a bath of metals, liquid at the working temperature and impermeable to hydrogen, can be used (Fig. 25, scale as in Fig. 24). In this case, however, the separating steel tube is decarburized through its entire wall and loosened at the grain boundaries, hence mechanically completely destroyed.

I now come to the *design of the convertor.*

It was obvious from the outset that the economy of the process necessitated extracting a large proportion of the heat required for heating the gas mixture by exchange from the exhaust gases. Yet the yield of ammonia after a single pass over the contact catalyst was only about $\frac{1}{6}$ of the original mixture.

Although at the beginning of our tests we had counted on compensating for the heat losses by heating the convertor, even with this arrangement the utmost economies had to be made since the amounts of gas passing through are enormous and the heat has invariably to be supplied to the hottest point before the catalyst. Moreover, care had to be taken to avoid an excessive temperature gradient owing to the passage of heat through the convertor jacket since in any case at the temperatures prevailing the strength of steel drops markedly, as shown in Fig. 26. In view of the low conversions involved we dared not count on replacing the heat losses by the heat of reaction alone.

Based on Knietsch's well-known design for the sulphuric acid contact process, the convertor was conceived as shown in Fig. 27. The design reproduced here for the ammonia convertor incorporates all the characteristics of the best modern tube convertor, the heat of reaction being removed as evenly as possible. The counter-current principle in the heat exchange has been retained

without modification. The admission of cold gas at the top enables the reaction to be controlled. The contact chamber is largely subdivided by the regenerator tubes.

At the time the design was shelved because the knowledge that the material is destroyed by hydrogen imposed the need for simplification. Copper regenerator tubes had been thought of and as transpired a few weeks later copper is particularly severely attacked by hydrogen (cf. Fig. 19).

As we were unable to incorporate the whole of the necessary heat exchangers in a convertor, two further regenerators were arranged in front of the contact tube so that the whole arrangement then appeared as shown in Fig. 28. Apart from the cluster of regenerator tubes in the convertor, this design also features a vertical cluster of regenerator tubes connected to a double spiral. The tubes between the convertor and the vertical regenerator were lined. The double spiral, too, was later dropped because the temperatures arising in it led to destruction by hydrogen and its resistance to flow was very high. A second vertical regenerator then replaced the double spiral.

The contact tube was heated on the outside using gas. With this apparatus quite prolonged operation was possible for the first time. But the hope that we were now at the end of all our difficulties was not fulfilled. Even without being destroyed by hydrogen, the steel jackets of the convertors were in the long run unequal to the high pressure at the high temperature imposed by the external heating. They buckled and cracked and the result was a series of heavy explosions which we were able to render harmless of course by accommodating the tubes in explosion-proof chambers but the continual high repair costs threatened the economics of the process. A different answer had thus to be found and consisted in supplying the heat from inside. Even then we still did not trust electrical inside heating as we were faced with unavoidable high losses to avoid overheating of the jacket. We thus tried gas heating by burning hydrogen (synthetic gas) with admitted air in the convertor. A certain amount of water was formed but did not appear to harm the contact catalyst. At any rate this was the lesser evil.

To avoid the risk of an explosion of the hydrogen–air mixture with every expectation of its being extremely violent, we studied the problem on the arrangement shown in Fig. 29. The flame in the pressureless apparatus was a pale greyish blue, at a pressure of 100 atm. the flame appeared a shiny bright blue.

The ultimate version of a convertor appeared as in Fig. 30.

The figure illustrates the design of a large convertor of 800 mm inside

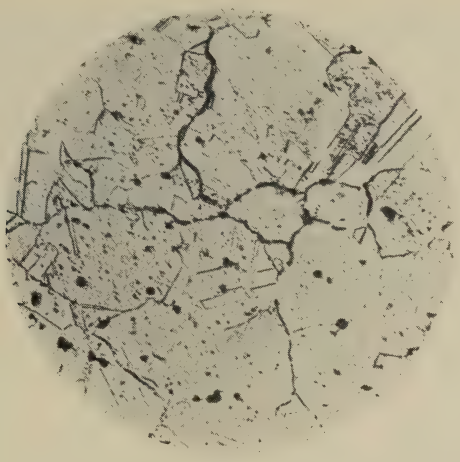
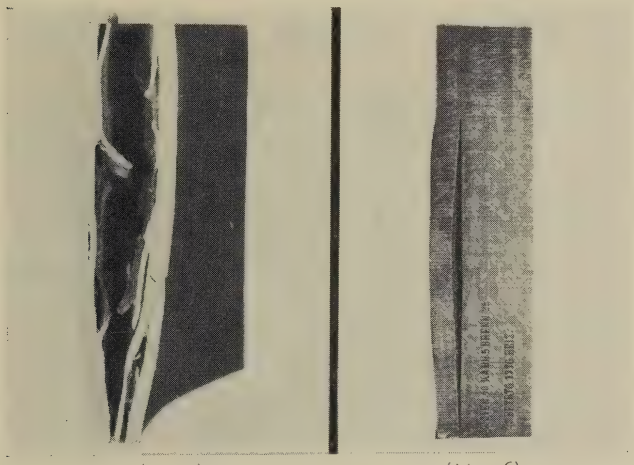


Fig. 19. Structure of copper tube destroyed by hydrogen. (×36).



(×0.3) (×0.16)

Fig. 20. Cavitation of sheet iron and rolled stock, 1913.

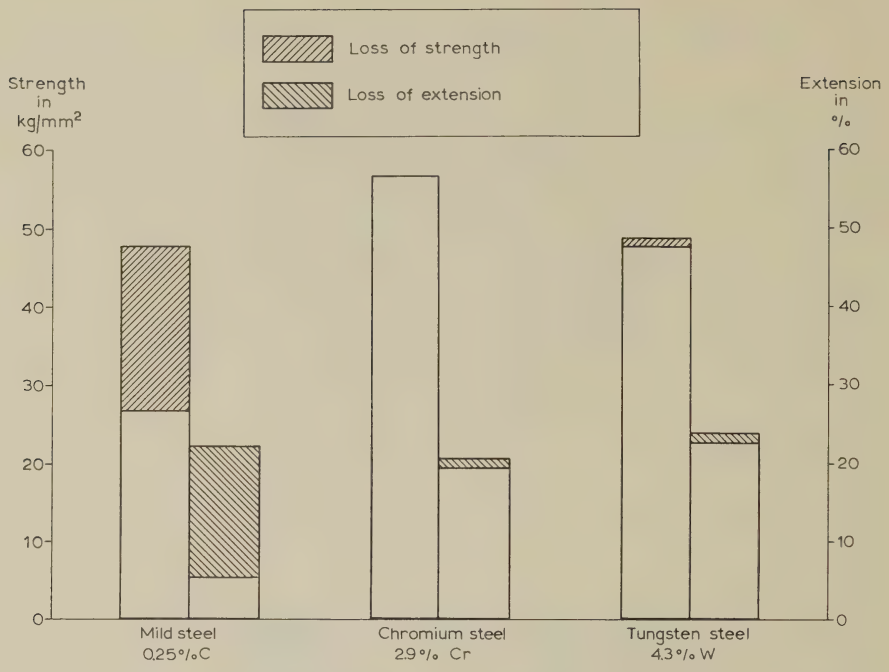


Fig. 21. Loss of strength and extension after treatment for 24 hours in hydrogen at 580° C and 150 atm., 1911.

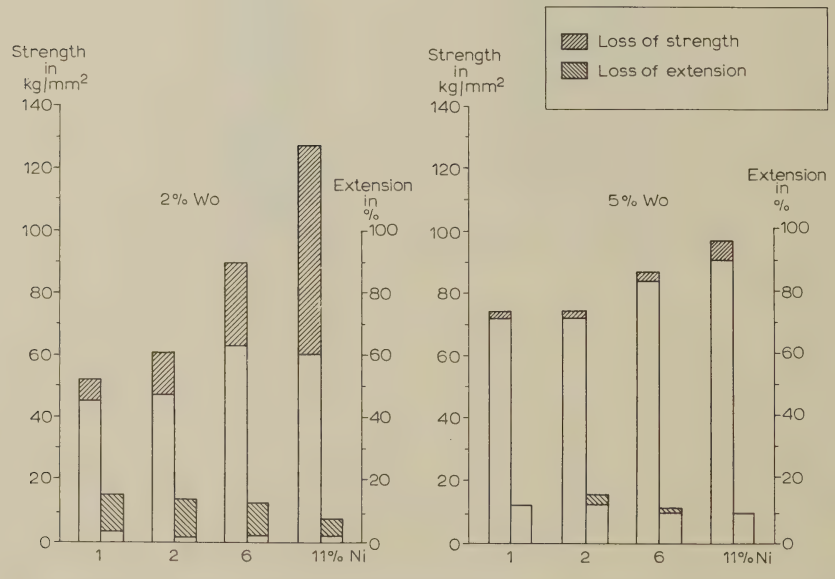


Fig. 22. Effect of nickel content on hydrogen attack on nickel tungsten steel, 1916.

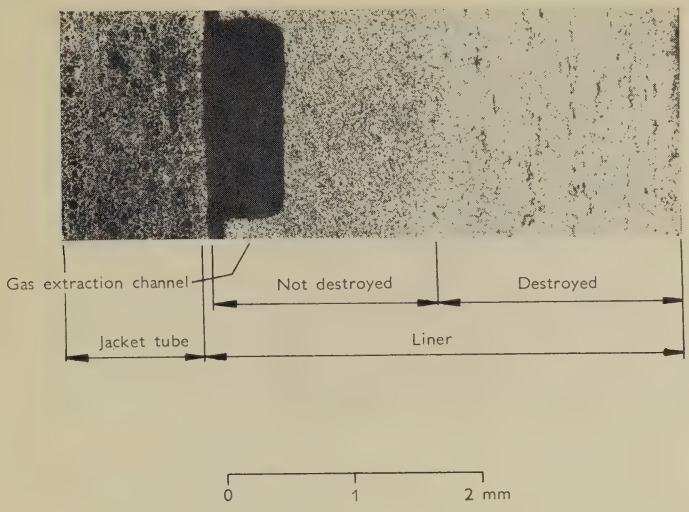


Fig. 23. Fine structure of a liner with degasification channels, 1910.

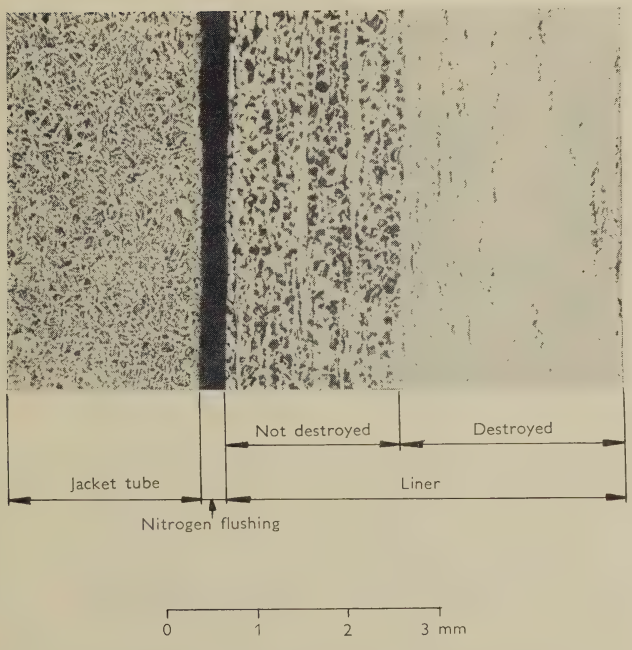


Fig. 24. Protection of jacket by neutral gas.

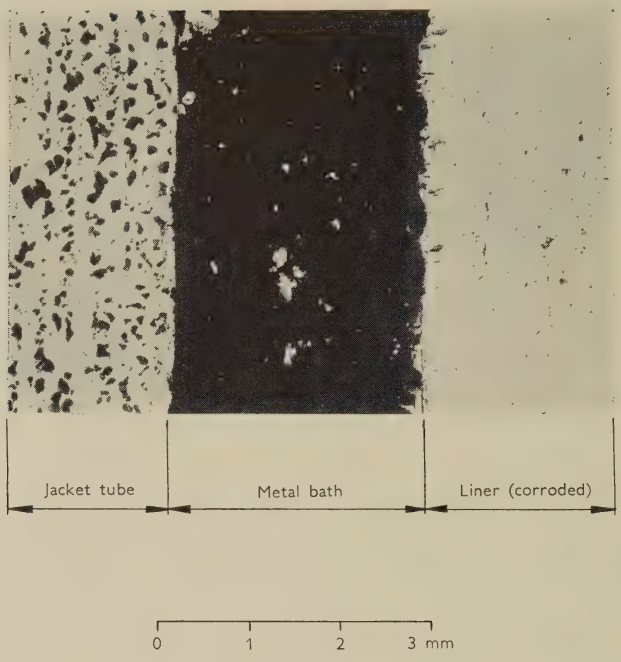


Fig. 25. Protection of jacket by metal bath.

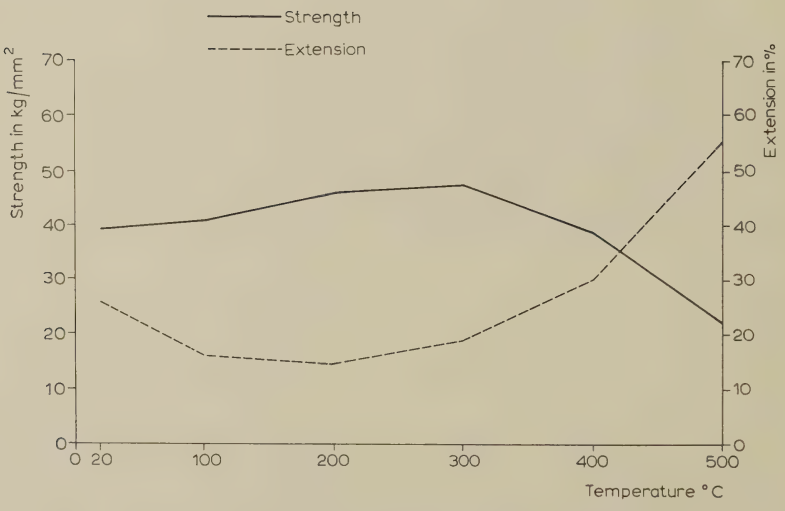


Fig. 26. Tensile strength and extension of mild steel (Bach, 1904).

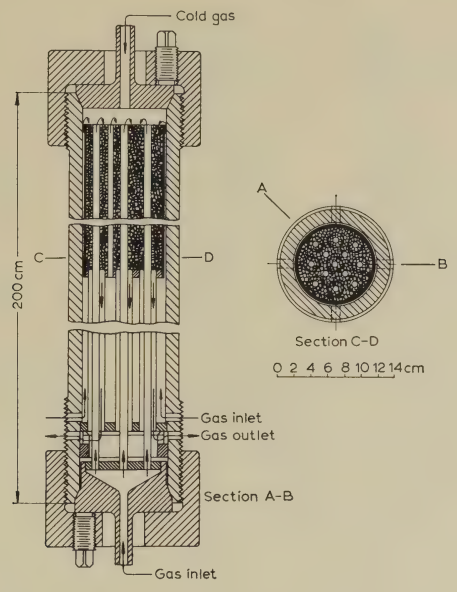


Fig. 27. Convertor, 1910.

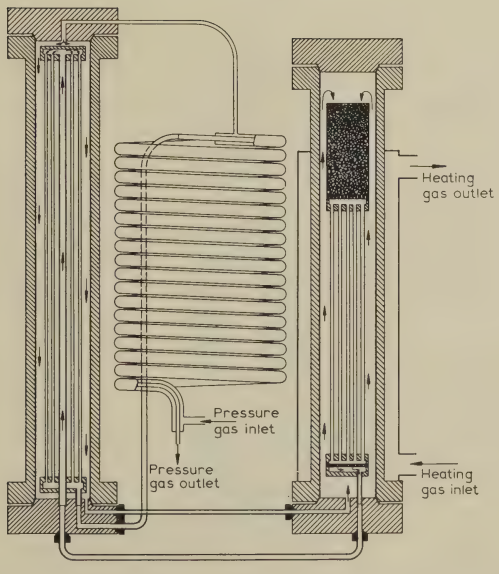


Fig. 28. Convertor with heat exchanger and external gas heating, 1911.

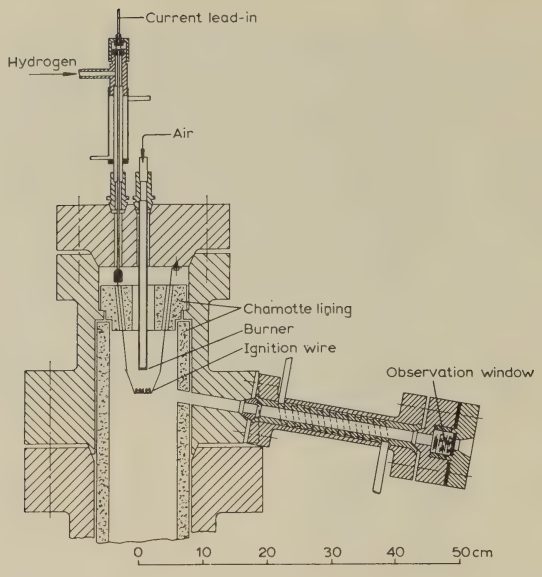


Fig. 29. Experimental apparatus with internal gas heating under pressure, 1911.

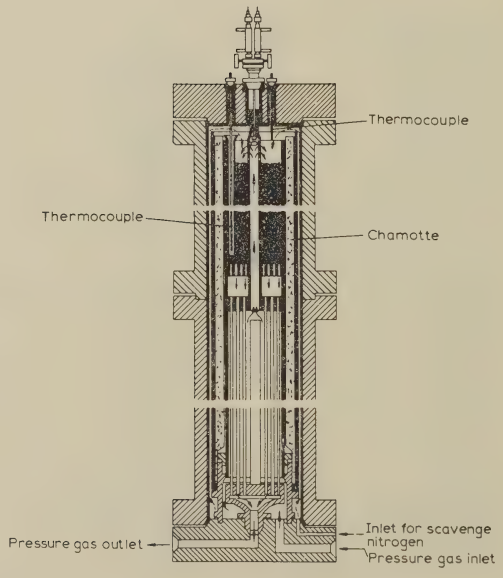


Fig. 30. Convertor with nitrogen flushing, 1916.

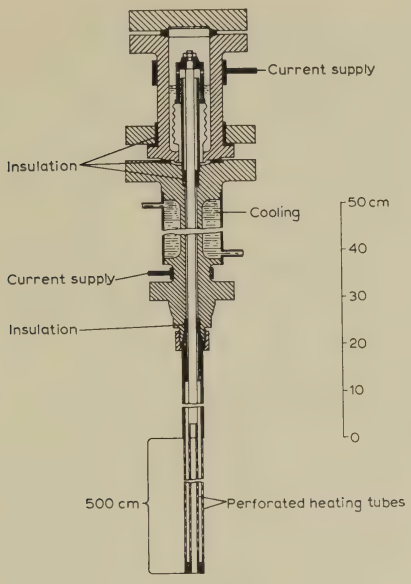


Fig. 31. Electrical burner, 1918.

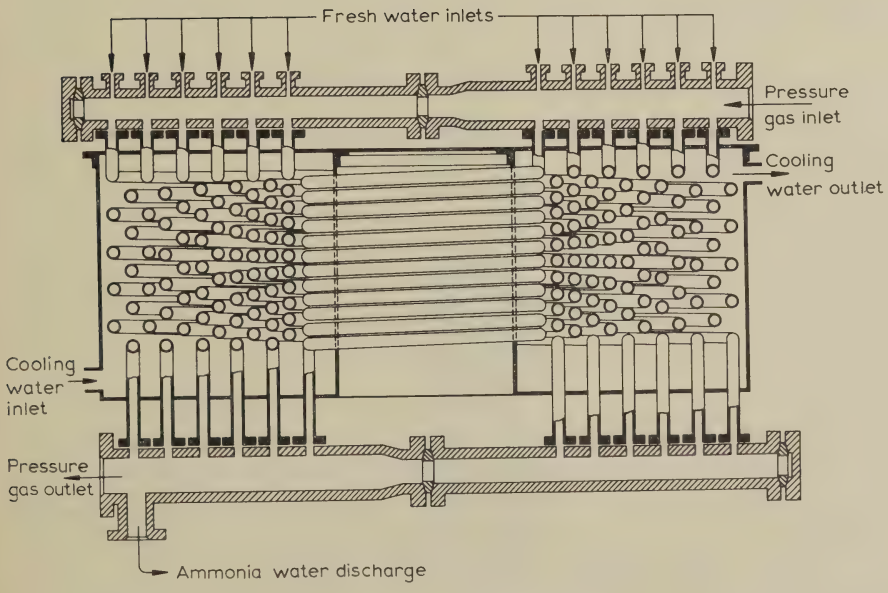


Fig. 32. Coil absorber, 1913.

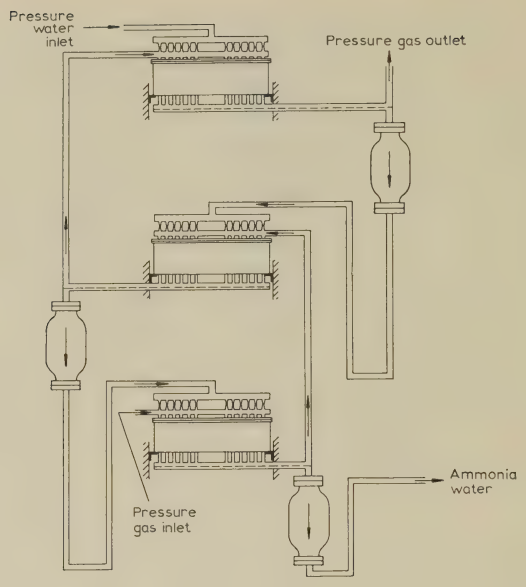


Fig. 33. Coil absorption, 1915.

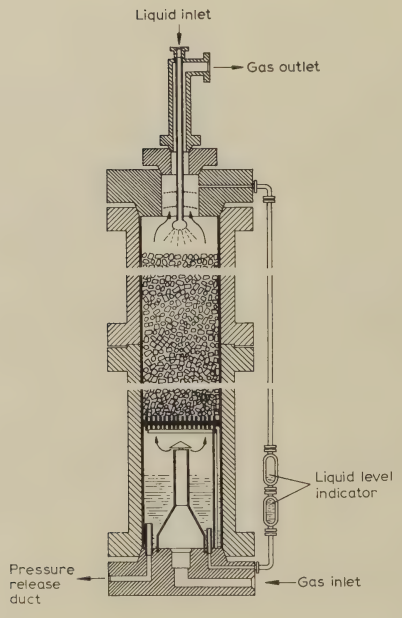


Fig. 34. Large ammonia absorber, 1920.

diameter – an « 800 oven » – with gas heating on the inside, a central tube and nitrogen flushing. The inside system of gas heating was retained until 1922. During the more than 10 years that this method was used under production conditions, no explosions occurred in the convertors. Observations of the thermocouples, particularly the one fitted to the burner, showed when it was necessary to apply additional heating to the oven, even below a pressure of 200 atm., by forcing in air.

As we moved to bigger and bigger production units it was found that beyond a certain size it was possible, given good heat exchange, to offset the heat losses by the heat of reaction. This represented quite a considerable advance for then we were able to dispense entirely with continuous heating during the operation. It was just a matter of bringing the convertor to the correct initial reaction temperature. Gas heating had essentially the drawback that during the heating-up period the gas circuit had to be reversed with respect to normal operation in order to keep the combustion products away from the contact area, often causing stoppages owing to cracks in the convertor lining. Moreover the heat had to be applied across a high gradient to the gas at a relatively small point. These drawbacks were overcome by the electrical heater, about 5 m long, accommodated in the central tube (Fig. 31).

As the design of the convertors advanced we also turned our attention of course to the other parts of the high pressure apparatus. There was firstly the matter of withdrawing from the circuit the ammonia formed. The answer was to use water in the following way:

To prevent the entailment of water, water and gas flowed in the same direction through a spiral tube system cooled on the outside (Fig. 32). However, to achieve a counter-current and obtain the maximum concentration of ammonia water with the optimum scrubbing effect, three such systems were stacked one on top of the other which then operated on the counter-current principle (Fig. 33). Later it was learned how to build simple scrubbers (Fig. 34). This was an obvious answer but only practicable after long experience.

To-day, to cut down transport costs, a large part of the ammonia is liquefied free from water by intense cooling.

Initially the high pressure compressors were a great source of worry. Hitherto large compressors had only been used in engineering for compressing air. In the main they were used to produce compressed air for running compressed air locomotives in mines and for Linde type air liquefaction plants. These compressors were only designed in modest sizes. The chief trouble, however, was that little attention had been paid to the stuffing boxes. In the case of air,

leaks were not important and a brief stoppage was accepted. Matters are different where hydrogen and the sensitive contact process are concerned. Losses of hydrogen mean money and the risk of explosion, and the contact apparatus could not stand stoppages. Probably all the designs then built were tried out by us and in years of work, on the basis of the experience which we gained from those small compressors which ran for not more than half a day without stopping, we succeeded in building the gigantic 3,000 horse power units which function reliably and without stoppage for 6 months, after which they receive their regular, periodic clean. At this juncture I should like to stress how important completely smooth running is for the synthesis of ammonia. Every stoppage at a single point affects the entire plant and after a stoppage it takes hours until everything is back to normal. It is no exaggeration for me to say that, technically speaking, it depends entirely on smooth, continuous operation whether the process is economical. It has taken us years to reach that point. Of particular assistance here were the *monitoring instruments* to which we turned our attention right at the outset since it soon transpired that it was possible to follow the events in the convertors only by continuous recording. Nowadays that is obvious and most of the instruments are even available commercially but in those days we had to build and try them all out ourselves. Of the abundance of characteristic examples I shall deal only with a few. Besides accurate temperature monitoring at all points in the convertor by simple thermocouples, and the determination of the ammonia, the main factor of interest is the intensity of the gas stream. A *pressure balance*, as it is termed, permits measurement of the gas stream with the maximum precision at the highest pressures (Fig. 35). Measurement of the amounts of gas, steam and liquid under high pressure necessitates recording the pressure difference arising in the jets or orific plates in the pipe line, the square root of which is proportional to the amount. The pressure balance records these square roots by means of a semi-circular, U-tube housed in one of the balance arms and half filled with mercury. The pressures prevailing in front of and behind the orifice plate are applied to both ends of the balance via elastic capillary tube solenoids. The square of this value is plotted on a cylinder via a swinging lever fitted with a guide.

The composition of the circulating gas stream also has an important bearing on the process. It is indicated by the automatic *density recorder* (Figs. 36 and 37). The density recorder is based on Bunsen's law relating to flow and both controls the proportion of the mixture of hydrogen and other gas admixtures, and accurately records the gas density which has to be allowed for when the

amount of gas is measured by means of a jet. Errors induced by temperature and pressure are compensated by comparing the flow volumes of the gas mixture and a standard gas (air) in the same times and at the same temperatures.

It is very important to monitor the process for any *oxygen* content, not only because of the explosion risk but also because of the steam created in the hot catalyst which, as we now know, reduces the yield.

The procedure here is as follows (Fig. 38). To record small contents of oxygen down to 0.01% the hydrogen mixture is guided through an electrically heated combustion tube with a differential thermopile, the even numbered junctions of which carry collars of catalyst of minimum thermal capacity where the reaction

$$O_2 + 2H_2 = 2H_2O$$

produces a temperature rise with respect to the uneven numbered junctions. The thermoelectric current generated is recorded and trips an alarm on reaching a given danger level. With the addition of electrolytic hydrogen the instrument records the oxygen content of Linde nitrogen. It is used also for other exothermic reactions, e.g. to detect benzine vapour in the air.

No less attention had to be paid to monitoring the carbon monoxide content since next to sulphur this is the greatest enemy of the iron contact catalyst.

The water–gas equilibrium, which in our process at low temperature and with excess water vapour we displace to the right hand side of the equation

$$CO + H_2O = CO_2 + H_2$$

is at about 2% CO under technical conditions.

After the carbon dioxide has been removed by scrubbing with water under pressure, carbon monoxide is removed by means of an ammoniacal solution of cuprous oxide. The carbon monoxide dissolved in this solution is driven off by gentle heating and reduction of the pressure. A solution containing just cuprous oxide precipitates metallic copper since carbon monoxide has a slow reducing action. To avoid that effect a little oxygen is continuously added to maintain the solution at an accurately controllable concentration of cuprous oxide. The apparatus used is that shown here (Fig. 39). The apparatus monitors the degree of oxidation of the cuprous oxide solution which absorbs the carbon monoxide. The blue cupric ions of the solution flowing through

the cell absorb part of the light from an incandescent lamp striking a thermopile. The difference between the thermoelectric power of this thermopile and a second one irradiated via a standard filter is recorded. It is approximately proportional to the cupric ion concentration and thus to the amount of oxygen taken up by the solution.

The construction of such a large interconnected apparatus as at present installed in our works at Oppau and Leuna and the thousands of metres of tubing, and the thousands of flanges and valves associated with it also necessitates a special study, of course. Above all, everything has to be gas-tight and the appropriate measures have been so successful that the gas losses are just sufficient to prevent the argon content originating from the air and the accumulating methane attaining too high a level in the circulating system.

The apparatus has to be perfectly reliable and permit extremely rapid shut down and evacuation of parts in the event of stoppages. Over the years we have been able to cull sufficient experience, especially during the war when the Oppau works were bombed night after night, and we are still of the opinion today that one cannot be too careful. Consequently we have always played for safety, and ultimately took over ourselves the design and a major part of the manufacture of the fittings in our own workshops. Apart from seamless tubes, only steel forgings are used. Briefly I should like to cite a few examples (Figs. 40, 41 and 42).

In the quick-acting valve (Fig. 40) the magnetic coil mounted on a compression-resistant jacket of V2A non-magnetic steel is energized by contact manometers operating on the steady flow principle, in the event of a tube breakage. The self-closing valve (Fig. 41) with spring release and by-pass valves is automatically sealed off at one side or the other by the gas stream when the rate of flow becomes too high owing to tube breakage.

The slide valve illustrated in Fig. 42 which is designed as a venturi tube is rapidly closed in the event of tube breakage by the descending piston and by the release of pressure via the needle valve on the adjustable pin. When the exhaust channel milled in the slide valve pin enters the false bottom, the closing action is retarded. Two circulating pumps (Figs. 43 and 44) are worthy of mention as examples of further important new designs. The design in Fig. 43 is marked by the passage of the piston rod through the cylinder head to prevent as far as possible deposits of liquid and dust settling on the stuffing box. The feature of the rotating gas circulating pump (Fig. 44) is that the electric motor and the centrifugal pump function in a pressure vessel at 200 atm.

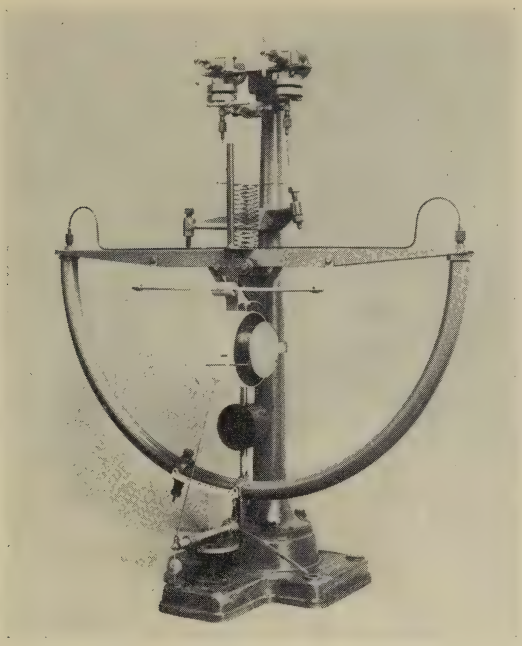


Fig. 35. Mercury pressure balance for gas, 1914.

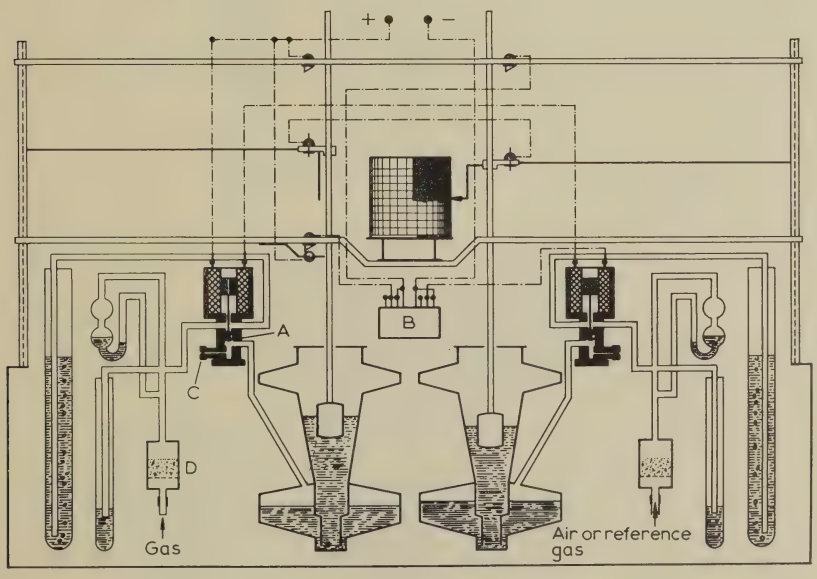


Fig. 36. Gas density recorder (*A* = three-way valve; *B* = d.c. relay; *C* = gas jet; *D* = filter), 1914.

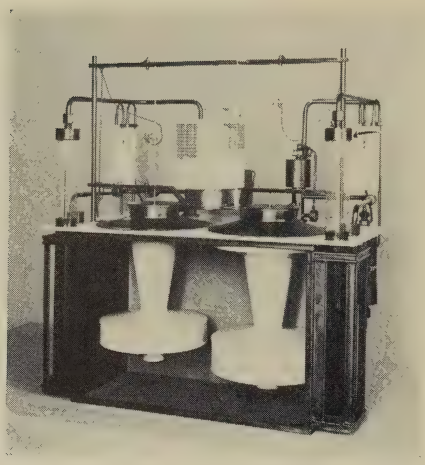


Fig. 37. Gas density recorder, 1914.

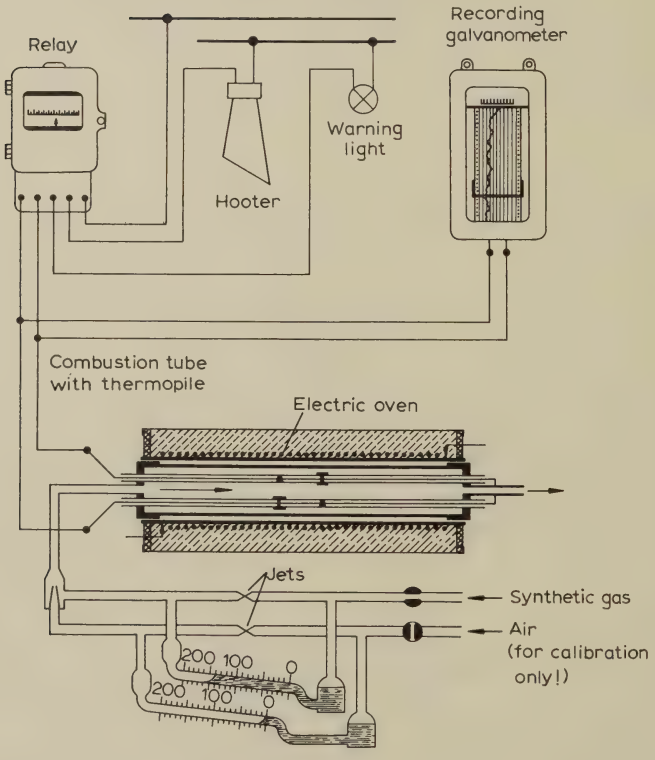


Fig. 38. Instrument to detect traces of oxygen by thermal effect, 1919.

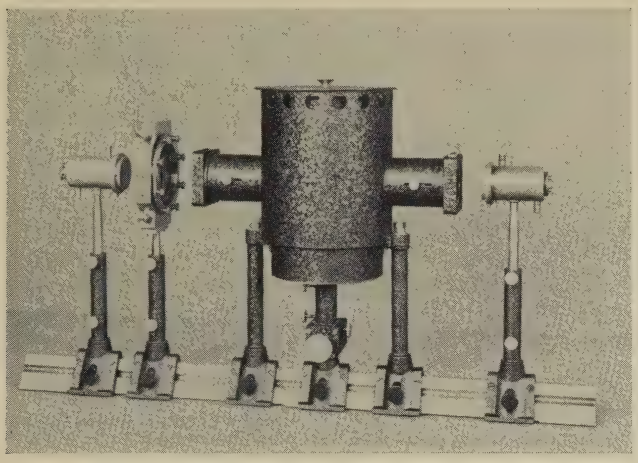


Fig. 39. Colorimeter to measure oxygen in copper solution, 1921.

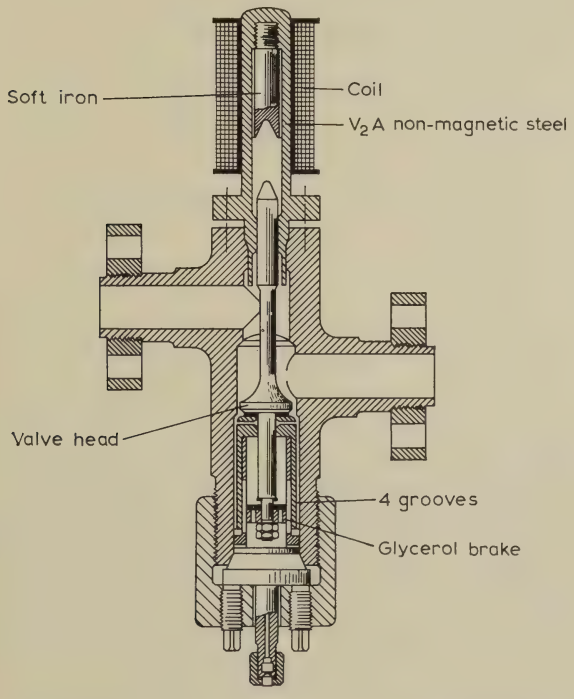


Fig. 40. Magnetically operated quick-acting valve, February 1913.

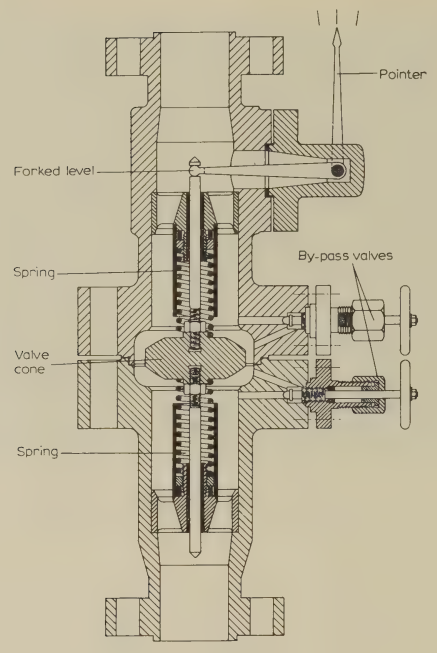


Fig. 41. Self-closing valve, October 1912.

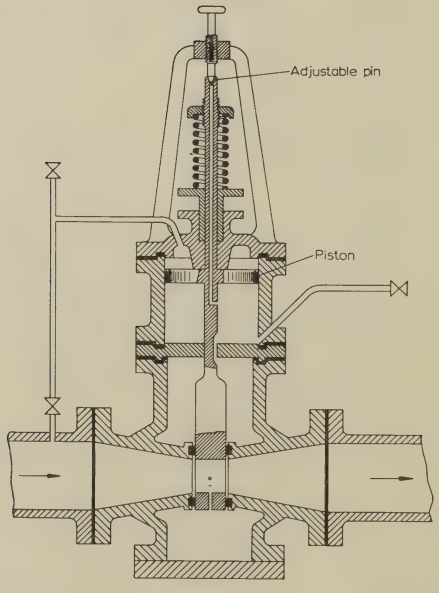


Fig. 42. Quick-acting slide valve, 1926.

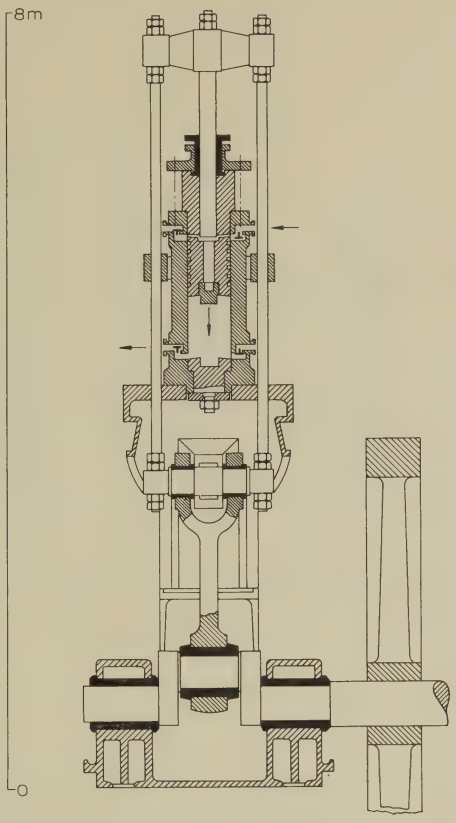


Fig. 43. Large piston circulating pump.

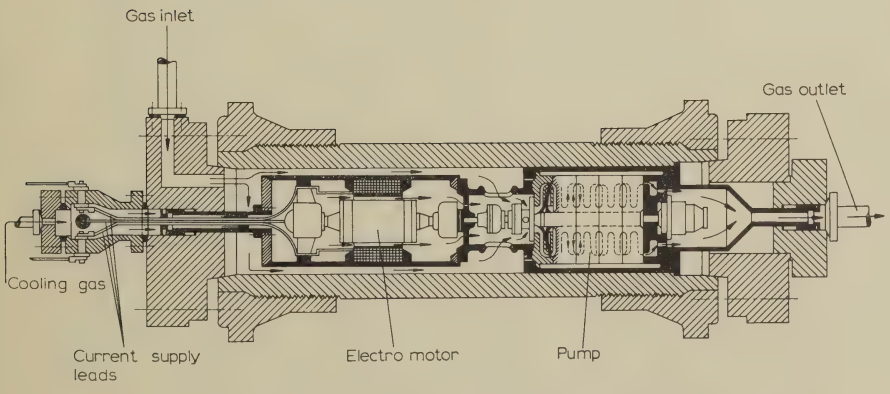
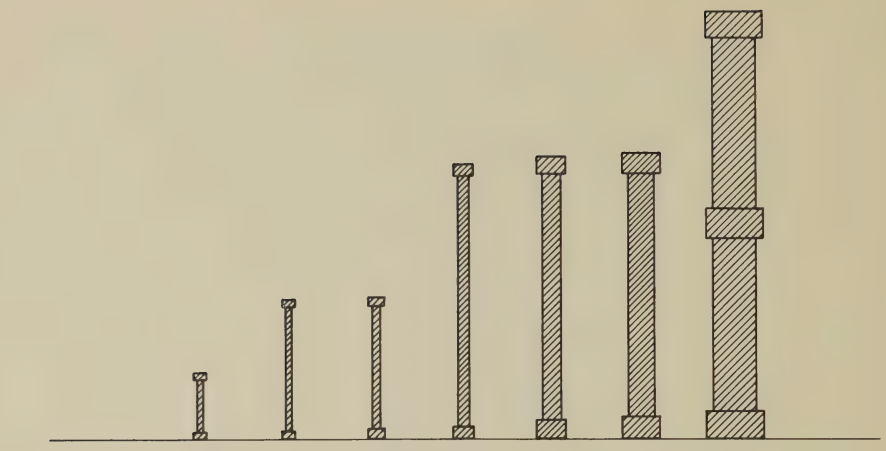


Fig. 44. Rotary gas circulating pump, May 1922.



Year:	1910	1911	1912	1913	1913	1914	1915
Diameter in mm:	146	146	230	285	450	675	1080
Length in m:	1.8	4	4	8	8	8	12
Weight in t:	0.3	0.5	1	3.5	8.5	25	75

Fig. 45. Increasing size of ammonia convertors, 1910–1915.

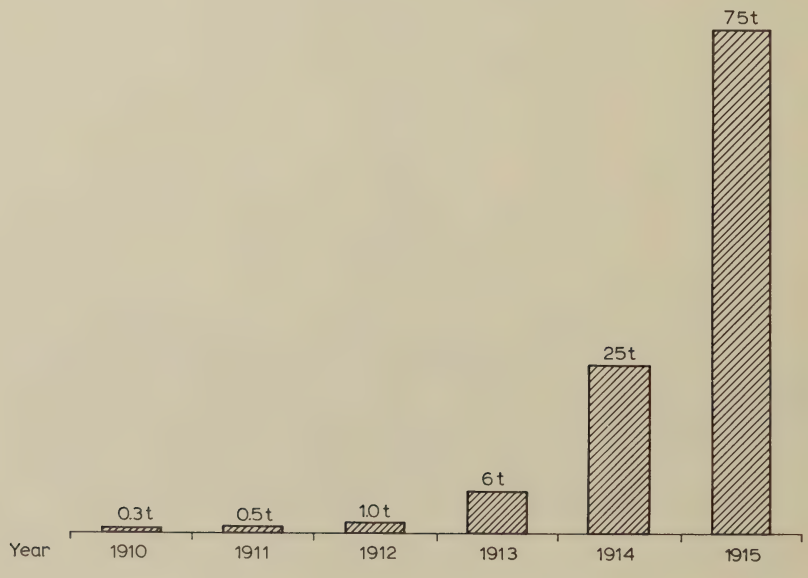


Fig. 46. Increasing size of ammonia convertors, 1910–1915.

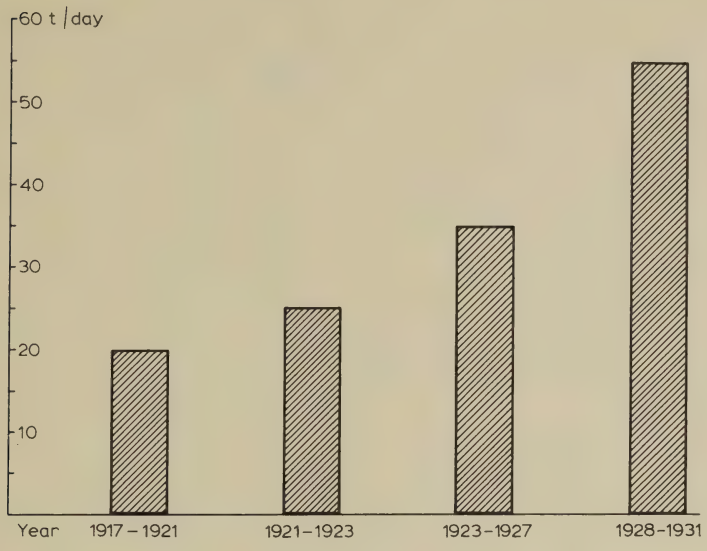


Fig. 47. Output of large convertor in tons of nitrogen per day, 1917–1931.

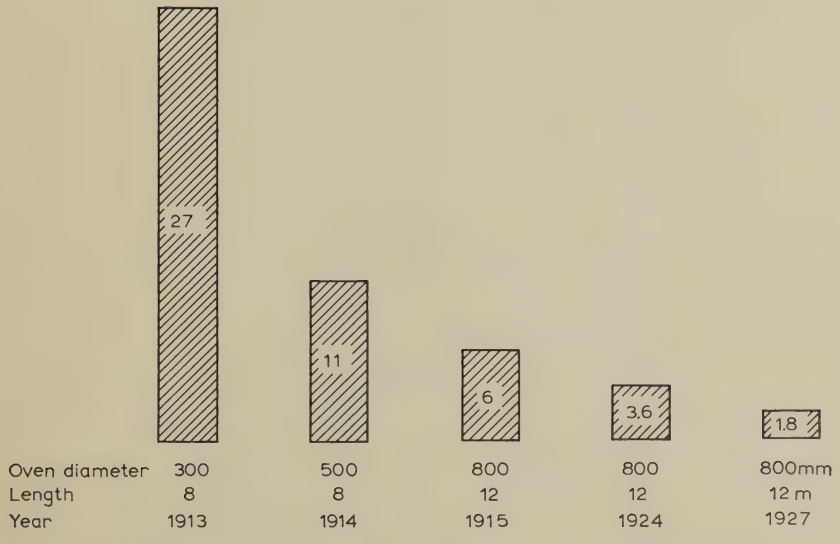


Fig. 48. Weight of steel for equal production of nitrogen, 1913–1927.

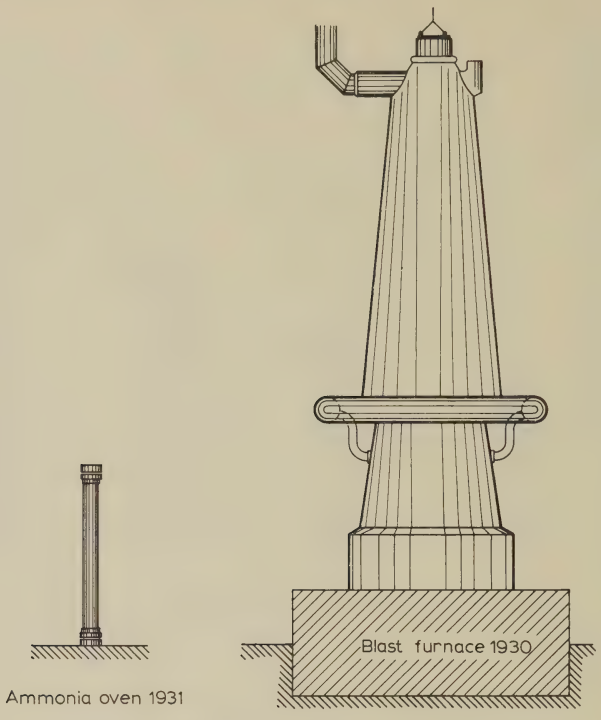


Fig. 49. Comparison of sizes of blast furnace and ammonia convertor for same throughput value, 1930.

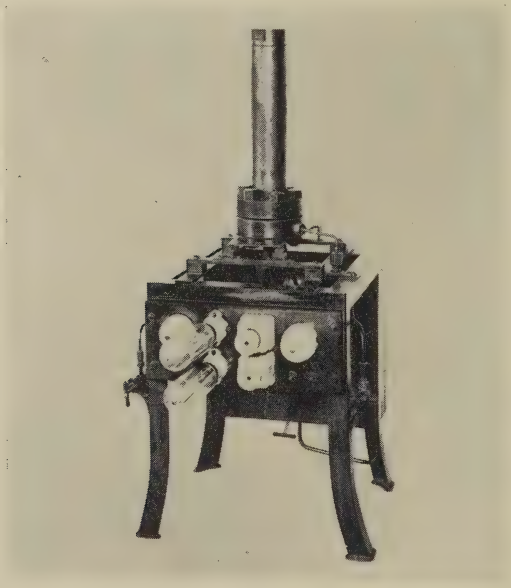


Fig. 50. Laboratory convertor, 1910.

In broad outline that is how the high pressure process for the synthesis of ammonia developed.

As a further illustration of the developments that have come about over the years I would like you to compare a few figures: Figs. 45 and 46 *vs.* Fig. 47.

The increase in the capacity of the large convertor from 1917 to 1931 (Fig. 47) was achieved by altering the design of the lining, improving the material and improving the gas purification. The reduction in the weight of steel for the same output of nitrogen (Fig. 48) was accomplished through improved design, better lining material and better gas purification.

Fig. 49 gives a comparison between a blast furnace and an ammonia convertor.

Figs. 50–59 incl. are a further few photographs which illustrate the trend of progress from the first test convertor to the enormous Leuna works.

I am now coming to the end of my account. The development of the ammonia manufacturing process which partly as a result of Germany's isolation owing to the war, was perfected in a relatively short space of time by harnessing all our efforts and resources, has also of course stimulated the development of other reactions which proceed markedly better under high pressure than under atmospheric pressure. Experience has shown that in general it is often much more economical to operate at high pressure but even when the technical high pressure synthesis has been mastered, measures must be taken to ensure that the partial pressures, whether of the reaction gases or of the impurities, are correspondingly high.

Let us assume that 0.01% CO has to be removed from a gas mixture. Technically, at the high speed of the gas flow and low pressure, this is practically impossible by scrubbing with an absorbent, but very easy at 200 atm. with a carbon monoxide partial pressure of 1/50 atm.

Right at the outset of our studies we looked into the reduction of carbon monoxide with hydrogen and found that liquid reaction products could be obtained which proved to be mixtures of aliphatic alcohols, aldehydes, ketones and acids derived from them.[7] Not until later (early 1923) was it realized[8] that the first reaction product, *methyl alcohol*, is only formed in quantity if gas free from iron carbonyl and iron-free contact catalysts (particularly ZnO–Cr_2O_3) is used and the influence of iron vessel walls avoided as they condense methyl alcohol. The optimum operating conditions to achieve high yields of pure methyl alcohol were soon found, thereby facilitating the very rapid development of the synthesis, so that to-day methanol has become one of the cheapest

products of the chemical industry. Possibly the annual production by the high pressure method of synthesis is not less than 40,000 tons.

A further reaction which very soon claimed attention is the manufacture of *urea* from carbon dioxide and ammonia with the formation of water.[9]

When a mixture of carbon dioxide and ammonia or ammonium carbamate is heated to 130–140°C in a closed vessel, a mixture of urea and water plus carbon dioxide and ammonia is formed. The equilibrium is favourable at about 40% of the theoretical yield of urea. If such a mixture were allowed slowly to cool, the water formed would re-saponify most of the urea and so impair the yield. Furthermore the thermal economy would be very poor. We therefore separate the reaction mixture by distillation at high pressure by suctioning off the excess ammonia and the carbon dioxide using heated compressors and condensing the gases again above the solidification point.

Fig. 60 gives an illustration of the compressors used for that purpose. By this process we are able to produce about 40,000 tons of urea annually at our Oppau works.

Besides other, less important, pressure processes coal hydrogenation has attracted particular interest in recent years. As he will shortly report, Bergius had found that when coal is heated with hydrogen under pressure, large quantities of liquid reaction products are formed. In our laboratories it was subsequently ascertained that by using catalysts these reactions can be better controlled and may yield any products from light hydrocarbons to lubricating oil. After Bergius' basic patents had been acquired this process was introduced on a wide scale in Oppau and Leuna on the basis of our experience with the high pressure process and catalyst manufacture and currently provides 120,000 tons of benzine a year.

Most of the large oil companies also acquired the process for the hydrogenation of crude oils that are not readily processed. The present economic situation and the keen competition on the oil market have held up development. Nevertheless these processes are destined to play a very important part in the future.

Finally, I would like to draw your attention to another photograph (Fig. 61) of a large convertor in our coal hydrogenation plant. This shows the sizes we have reached (over-all length of convertor 18 m). Only on a mass production scale can these processes compete with the natural products.

I have to-day been able to inform you about only a small section of the work which has been carried out in our firm since 1908 in the field under discussion.

It scarcely need be added that this achievement has only been made possible by a large staff of colleagues. It is probably true to assert that such numbers have never before been engaged on one single problem. I sincerely wish to mention in particular two colleagues present here to-day who threw themselves heart and soul into our work from the very outset, namely Dr. Mittasch, head of the scientific laboratory, and Dr. Lappe who was in charge of technical development. To them I would like to acknowledge now my gratitude for their unstinting, loyal co-operation.

1. D.R.P., 292,615 (1912).
2. D.R.P., 249,447, Jan. 9, 1910, together with supplements.
3. D.R.P., 291,582 (1912); 298,199 (1913) and 306,333 (1916).
4. D.R.P., 254,571 (Febr. 12, 1911) and 256,296 (Sept. 6, 1911).
5. D.R.P., 265,295 (1912).
6. Zentralstelle Neubabelsberg, D.R.P., 290,877 (1913).
7. D.R.P., 293,787 (1913).
8. Various patents issued in 1923 and subsequent years.
9. D.R.P., 295,075 (1915) and 301,279 (1916) and others.

[For Figs. 51–61 incl., see pages 236–241.]

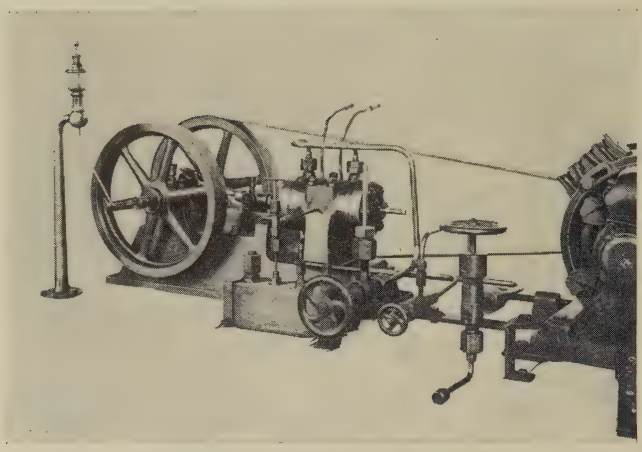


Fig. 51. Experimental circulating pump. August 1910.

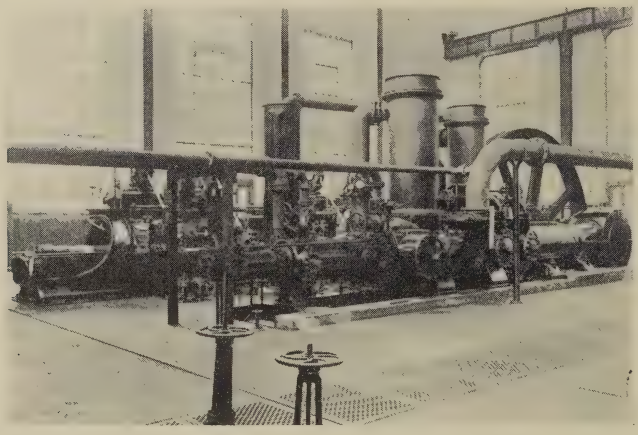


Fig. 52. High pressure compressor 1,000 h.p.

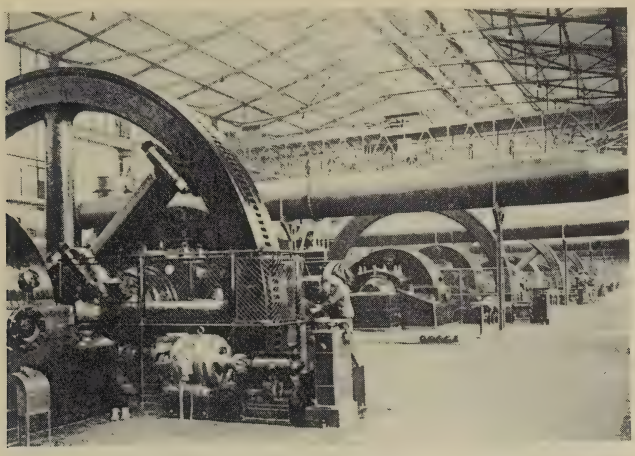


Fig. 53. High pressure compressor 3,000 h.p.

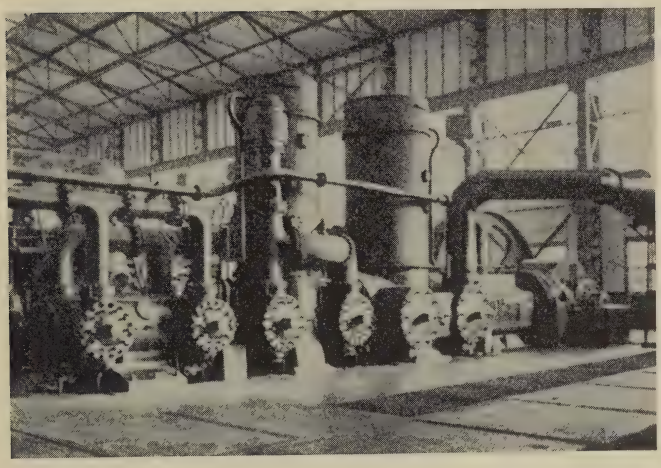


Fig. 54. High pressure compressor 3,000 h.p.

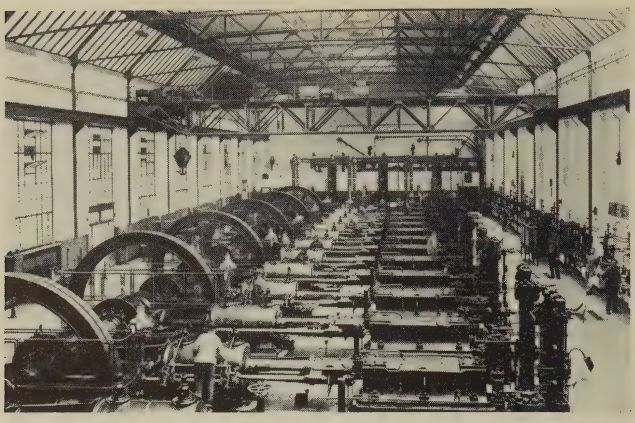


Fig. 55. High pressure lye pumps for gas purification.

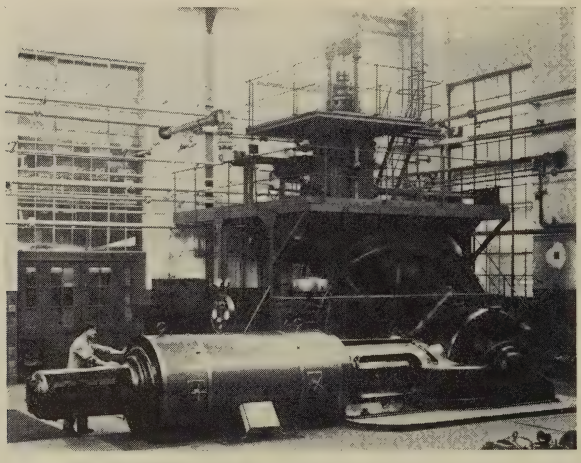


Fig. 56. Large piston circulating pump.

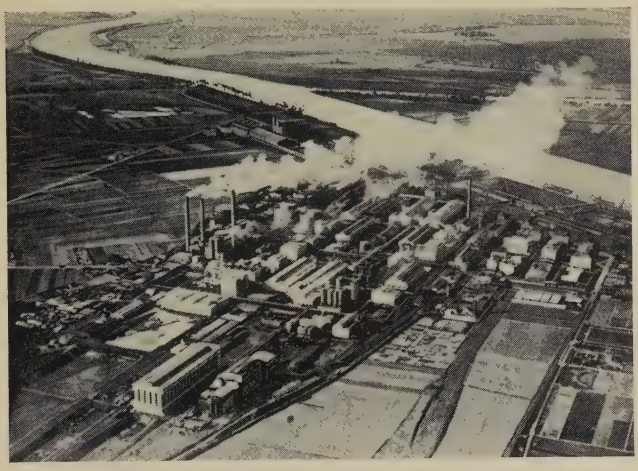


Fig. 57. Oppau works.

Fig. 58. Ammonia works at Merseburg.

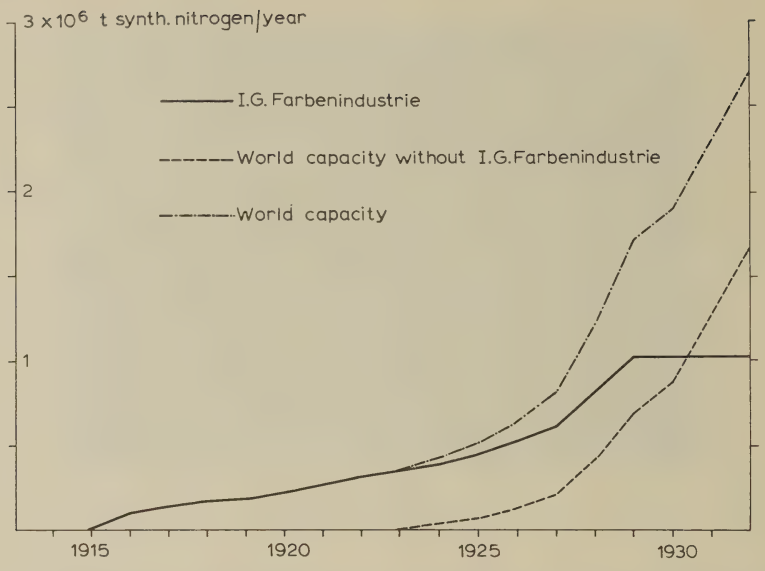


Fig. 59. World and I.G. Farbenindustrie annual capacity in tons of synthetic nitrogen.

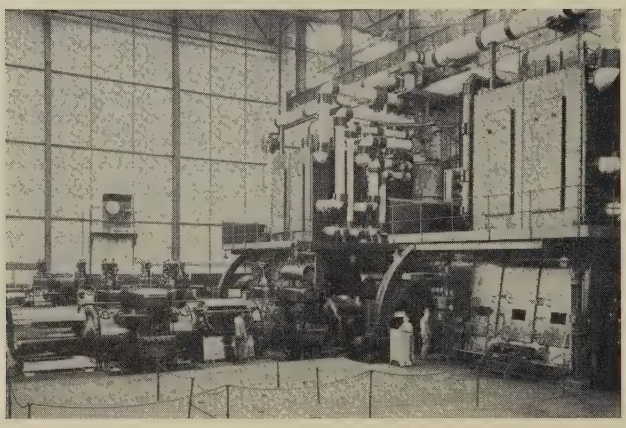


Fig. 60. Heated high pressure compressors for urea factory.

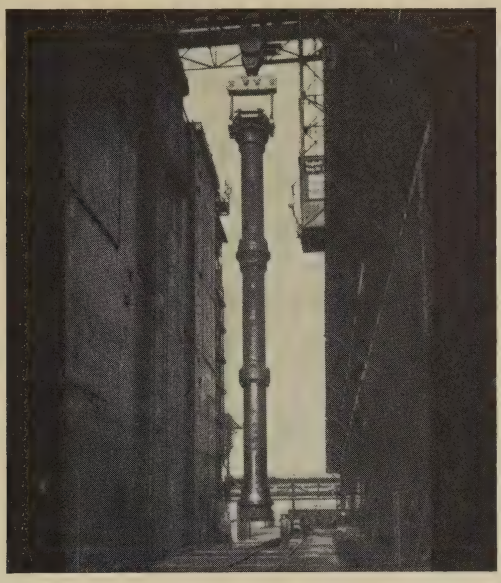


Fig. 61. Convertor and high pressure chambers of hydrogenation plant.

Biography

Carl Bosch was born at Cologne on August 27, 1874, and grew up there. From 1894 to 1896 he studied metallurgy and mechanical engineering at the Technische Hochschule in Charlottenburg, but started reading chemistry at Leipzig University in 1896. He graduated under Professor Wislicenus with a paper on organic chemistry in 1898. He entered the employ of the Badische Anilin- und Sodafabrik, Ludwigshafen/Rhine as a chemist in April 1899 and participated actively in the development of the then new industry of synthetic indigo under the guidance of Dr. Rudolf Knietsch.

At the turn of the century Bosch became interested in the problem of the fixing of nitrogen and his first experiments in this field were done with metal cyanides and nitrides; in 1907 he started a pilot plant for the production of barium cyanide.

Bosch's opportunity for really large-scale work came when in 1908 the Badische Anilin- und Sodafabrik acquired the process of high-pressure synthesis of ammonia, which had been developed by Fritz Haber at the Technische Hochschule in Karlsruhe. Bosch was given the task of developing this process on a large industrial scale. This task involved the construction of plant and apparatus which would stand up to working at high gas pressure and high reaction temperatures. Haber's catalysts, osmium and uranium had to be replaced by a contact substance which would be both cheaper and more easily available. Bosch and his collaborators found the solution by using pure iron with certain additives. Further problems which had to be solved were the construction of safe high-pressurized blast furnaces, a cheap way of producing and cleaning the gases necessary for the synthesis of ammonia. Step by step Bosch went on to using increasingly larger manufacturing units and thus created the industry which deals with the production of synthetic ammonia according to the high-pressure process.

From this work resulted the second task of making the thus won ammonia available for use in industry and agriculture. Bosch succeeded in working out methods for the industrial production of nitrogen fertilizers, thus providing practically every country in the world with sufficient fertilizers for

agricultural purposes. The Stickstoffwerke (Nitrogen Works) in Oppau were opened in 1913, followed by the even larger Leunawerke near Merseburg in 1917, where the synthesis of methanol and the hydrogenation of oil were added to the production programme. Bosch was appointed Managing Director of the Badische Anilin- und Sodafabrik in 1919 and in 1925 was made Principal of the I.G. Farbenindustrie Aktiengesellschaft, which was created by the merger of the German coal-tar dye works. In 1935 Bosch was appointed Chairman of the Board of Directors of the I.G. Farbenindustrie A.G.

Bosch was honoured in many ways and not only for his achievements and inventions in the field of industry, but also for his research in pure science, which he considered to be his duty. He received the honorary doctorate of the Technische Hochschule in Karlsruhe (1918), of the Landwirtschaftliche Hochschule (Agriculture College), Berlin (1921), the Technische Hochschule in Munich (1922), of Halle University (1927), the Technische Hochschule in Darmstadt (1928). The distinctions of Honorary Senator of the Universities of Heidelberg (1922) and Leipzig (1939), and of Honorary Citizen of Frankfurt (1939) were conferred upon him.

He received the Liebig Memorial Medal of the Association of German Chemists, the Bunsen Medal of the German Bunsen Society, the Siemens Ring, the Golden Grashof Memorial Medal of the VDI (Association of German Engineers), the Exner Medal from the Austrian Trade Association, and the Carl Lueg Memorial Medal from the Association of German Metallurgists. In 1931 he was awarded the highest international honour, the Nobel Prize for Chemistry, jointly with Friedrich Bergius, for their contributions to the invention and development of chemical high pressure methods.

Bosch particularly enjoyed his membership of various German and foreign scientific academies, and his chairmanship of the Kaiser Wilhelm Society of which he became its President in 1937.

He died after a prolonged illness on April 26, 1940.

Friedrich Bergius

Chemical reactions under high pressure

Nobel Lecture, May 21, 1932

Since the Royal Swedisch Academy of Sciences has considered my work on the development of high pressure methods for chemical reactions, and in particular work on the hydrogenation of heavy hydrocarbons and coal, to be worthy of the Nobel Prize, I wish to combine my gratitude for the high honour bestowed upon me with a report on the development of these systematic investigations and chemical researches to which my academic and industrial activities have been mainly devoted for almost 20 years.

The success of the first experiments with the high-pressure hydrogenation of oil and coal in the years 1912 and 1913 was due to the fact that the laboratory which I directed at that time in Hannover had already developed a method which permitted the conduct of a wide range of reactions in relatively easily operated apparatus at pressures up to about 300 atm and temperatures up to 450°.

In 1908 and 1909 I was given an opportunity in the laboratories of Nernst and Haber to witness the use of the high-pressure methods in investigations into the ammonia equilibrium and ammonia synthesis, and I tried my hand, in these laboratories, at that time, at syntheses by high-pressure techniques, with the then imperfect apparatuses, and with little success.

When, in 1909, I joined the physical-chemical laboratory of Hanover Institute of Technology led by Bodenstein, I decided to take up work on this new field which appeared promising to me on a wider scale, and developed, first in the laboratory of the Institute, and then in my own, relatively well-equipped private laboratory, assisted by several colleagues, of whom I would specially mention Hugo Specht, the methods and apparatus for investigating a number of diverse high-pressure reactions in the course of the years.

The problems in most of the investigations were mainly of a technical nature. Purely theoretical research was also done, but, if only for material reasons, to provide an economical justification for the private research laboratory, the principle of practical applicability of the problems studied had to predominate.

In our work, high pressure was used as a means for carrying out chemical

reactions in very different senses of the term. I reported on this in a monograph in 1912 (« The Application of High Pressures to Chemical Processes and Simulation of the Genesis of Bituminous Coal »)*. Ammonia synthesis had first availed itself of the possibility to influence *the position of the equilibrium* of a gas reaction in a certain direction by increasing the pressure. In our first detailed study into high-pressure reactions we applied the Le Chatelier principle to a heterogeneous system, i.e. to the study of *the dissociation of calcium peroxide*, whose dissociation pressure curve can, as a result of the slow rate of disintegration at low temperatures, only be measured in a temperature range at which the pressure of dissociation is already about 100 atm.

We made extensive use of the possibility, provided by high pressure methods, to conduct reactions between substances that are liquid at normal temperatures, i.e. at temperatures at which the vapour pressure of the substances concerned is very high, in other words to react liquids with one another at temperatures at which the substances concerned otherwise react only as gases and even then react very slowly or not at all with one another. This includes investigations into the *reactions of superheated water*, its influence on coal and iron and the *saponification of organic chlorides*, such as chlorobenzene and ethylene chloride with aqueous solutions of caustic alkali. In the end, we employed in the *hydrogenation of heavy petroleum and coal*, the increase in hydrogen concentration made possible by high pressure, and thus enabled acceleration of the rate of addition of hydrogen to the disintegrating oils and to coal.

Study of the dissociation of CaO_2

My main reason for mentioning the first series of experiments in 1910, the measurement of the *dissociation equilibrium of calcium peroxide*, is that it played a significant part in the development of our high-pressure work. The economical and technical starting-point of these researches was the interest which the production of peroxides and perborates had gained at the time. Production methods of hydrogen peroxide and its starting materials were anything but perfect. Engler and Becker had computed the dissociation conditions of calcium peroxide by means of Nernst's approximate formula and found that its dissociation pressure reaches 1 atm. at as little as 55°, and must rise to about

* *Die Anwendung hoher Drucke bei chemischen Vorgängen und eine Nachbildung des Entstehungsprozesses der Steinkohle*, Verlag Wilhelm Knapp, Halle, Germany.

100 atm at 170°. Our experiments showed that measurement of these dissociation pressures was only possible when the calcium peroxide was examined not in the solid state, but dissolved in the caustic potash–caustic soda eutectic. After lengthy efforts, we succeeded in obtaining fairly accurate measurement of dissociation pressures, starting both from the calcium peroxide decomposition side, and from the formation of oxygen and lime. In the end we also succeeded in converting lime in suspension in caustic alkali melt practically completely into CaO_2.

This observation has acquired no industrial significance, but it greatly assisted in the development of our high-pressure method: our problem was to keep apparatus, consisting of a decomposition vessel and a precision manometer, oxygen supply pipes and valves, completely leak-proof for several weeks at temperatures up to 400°. Since the capacity of the reaction bomb had

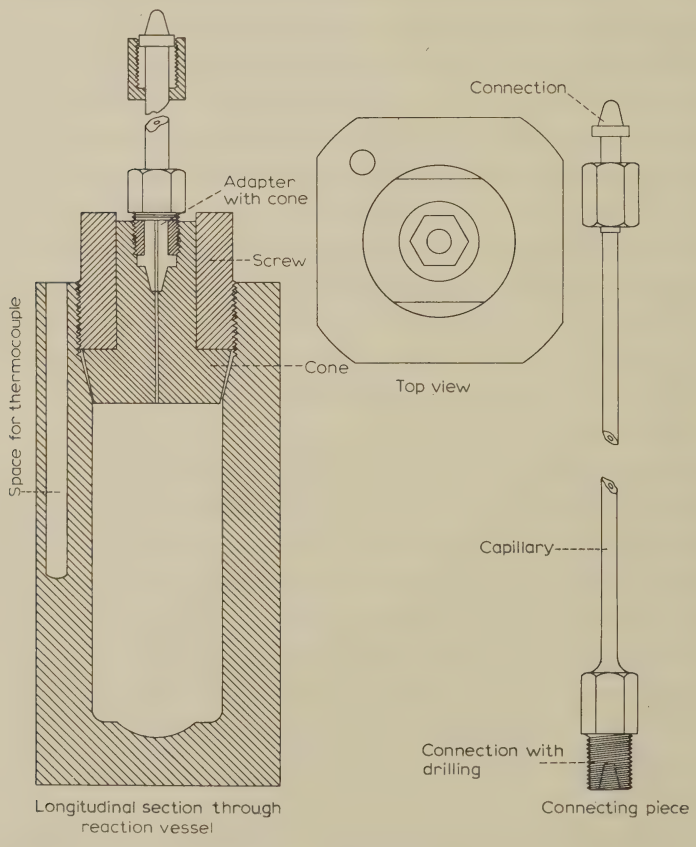


Fig.1. High-pressure experimental vessel, 1910.

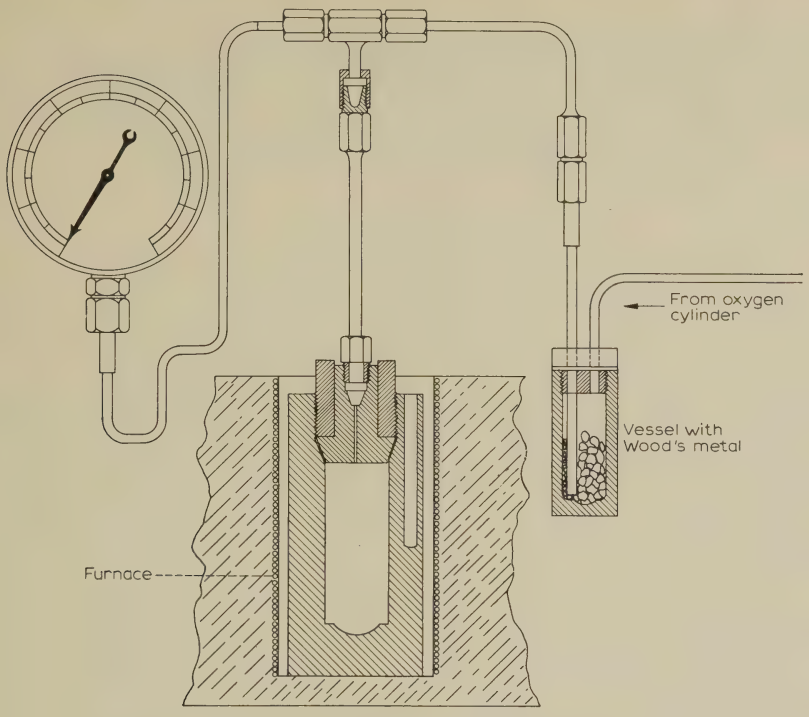


Fig. 2. Experimental vessel for peroxide equilibria, 1910.

to be restricted to a few hundred cubic centimetres, infinitesimal gas losses would have resulted in considerable errors of measurement during the weeks required for establishing equilibrium. Figs. 1 and 2 show the apparatus used. Pressure vessels of similar design and various sizes were used by us for years and may well still be suitable for small laboratory tests.

Even in the investigations into direct production of calcium peroxide in an alkali melt with highly compressed oxygen it was found to be necessary to bring the high-pressure gas into contact with the suspension of lime in caustic alkali melt by *agitation* or some other means of mixing. At that time, in 1911, experience was still lacking in the manufacture of pressure-resistant stuffing boxes suitable for sealing a relatively rapidly rotating agitator shaft. We built a pressure vessel having a small electromotor in its upper, cooled part, agitation taking place in the lower, heated part. To avoid the danger of highly compressed oxygen acting on organic substances, the small electromotor was to be fitted with windings of enamelled wire. The mechanic concerned however failed to carry out this instruction, and we had a very un-

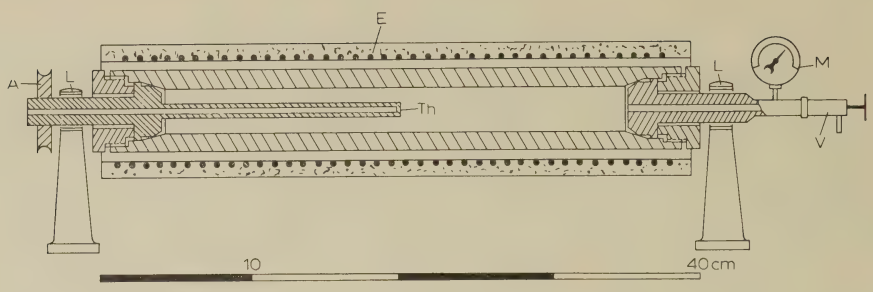


Fig. 3. Rotary vessel, 1912.

pleasant explosion. The quantity of insulating material in the tiny motor was infinitesimal, which did not prevent the part of the pressure vessel containing the motor from exploding on starting up, and the vessel with a wall thickness of about 30–40 mm was shattered which could have done considerable damage.

This experience spoilt our taste for working with highly compressed oxygen, but it furthered our cause in that we realized that such agitators are far too complicated and dangerous. In 1912 we therefore designed the extremely simple so-called *rotary bomb* shown in Fig. 3. A length of Mannesmann tube was closed at the ends with a high-pressure cone each, to which an extended shaft was attached. The shaft was supported in bearings and was driven by a chain wheel drive or a belt pulley. The pressure vessel rotated in an electrical oven. For temperature measurement, one of the cones had a central drilling, and a tube terminating in the reaction chamber accommodated a fixed thermocouple introduced from outside. Pressure was read on a manometer which rotated together with the apparatus. The design of this convenient apparatus acquired great significance for the further development of our

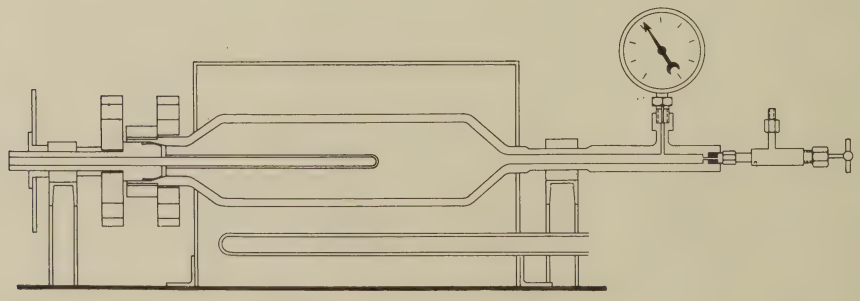


Fig. 4. 5-litre rotary vessel.

work, and we not only used it in our own studies, but made similar apparatus available to other research laboratories. It underwent numerous changes later; we ourselves used it in sizes from 250 cm^3 to 40 litres. Fig. 4 shows the 5 l vessel, which was mainly used at a later date.

Production of hydrogen

Work on catalytic hydrogenation and the development of technical hydrogenation reactions of hardening of fats and of the ammonia synthesis directed the attention of expert circles at that time to methods for the production of pure and cheap *hydrogen*. At that time, the process of the Badische Anilin- & Soda-Fabrik for the catalytic conversion of carbon monoxide of water gas into hydrogen and carbon dioxide was still unknown. The best available method for producing hydrogen seemed to be that according to Linde in which the carbon monoxide of the water gas was separated from the hydrogen by liquefaction at low temperatures.

In 1911 I conceived the notion that it should be possible to carry out the *water gas reaction*, which occurs at a technically satisfactory velocity and then according to the formula $C + H_2O = CO + H_2$ only at temperatures of the order of 900°, at considerably lower temperatures, at which the position of the equilibrium is practically such that the reaction corresponds to the formula $C + 2H_2O = CO_2 + 2H_2$.

The object therefore was to inhibit the troublesome formation of carbon monoxide completely. To achieve this aim, it would have been necessary to work at temperatures below 600°, at which steam practically ceases to act on coal. The aim was to discover whether, as it were by increasing the steam concentration, i.e. by using liquid water, the reaction velocity might not be increased sufficiently to adjust the equilibrium. In following this train of thought, the attempt had to be made to make liquid water react with coal in the vicinity of the critical point, i.e. at pressures of about 200 atm. This reaction was studied for a period of time with the apparatus according to Fig. 5, and we succeeded on a modest scale in oxidizing coal under these conditions into carbon dioxide and hydrogen, in particular when we dissolved metal compounds as catalysts in the water, the chlorides of thallium in particular proving successful. We failed however to achieve oxidation velocities which would have rendered technical exploitation of this reaction promising. Observations were however made in these experiments which were of importance

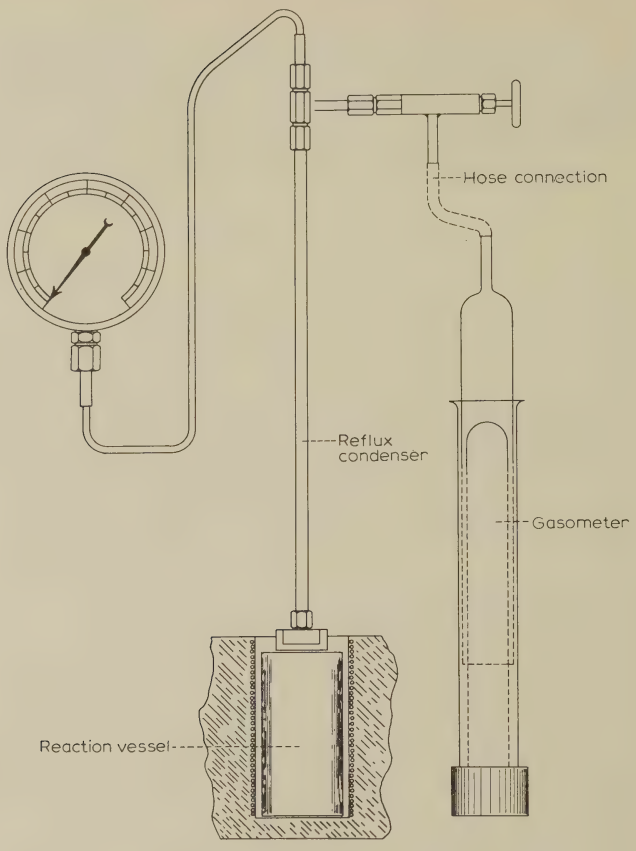


Fig. 5. Experimental vessel for high-pressure hydrogen from iron, 1911.

for our later high pressure work. When peat was used as coal material because of its finely distributed form on one occasion, it was observed that exceptionally large amounts of carbon dioxide formed, and that carbonaceous residue remained in the vessel whose elementary analysis approximated extraordinarily to the composition of natural flame coals. A closer study of this phenomenon revealed that what was involved was the coalification reaction, the reaction of the conversion of plant substance into coal, which became soon after the subject of prolonged investigations of importance for later developments, to which I shall revert below.

On the other hand it was discovered that under certain conditions the water containing metal salts greatly attacked the iron walls of the vessels with evolution of hydrogen. The latter phenomenon was investigated and it was discovered that it is possible to convert iron, treated in a suitable form with

liquid water at temperatures between 300 and 350°, almost quantitatively into Fe_3O_4 with formation of large amounts of hydrogen, and that this reaction progresses extremely rapidly. In these circumstances, the water acts as it were as an acid and is decomposed by the metallic iron. It was remarkable that this reaction by contrast with the effect of steam on iron at high temperatures is not a pure surface reaction, but that fairly finely distributed iron, e.g. filings, produces hydrogen with practically quantitative yield. The Fe_3O_4 could be reduced with coal or carbon monoxide gas and used for hydrogen

Fig. 6. Apparatus for producing high-pressure hydrogen.

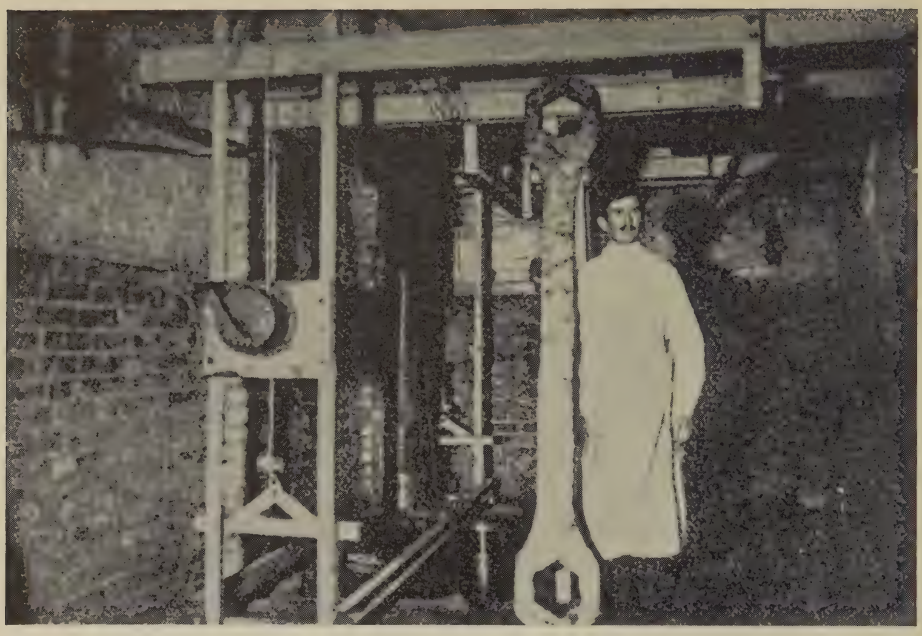


Fig. 7. Apparatus for producing high-pressure hydrogen.

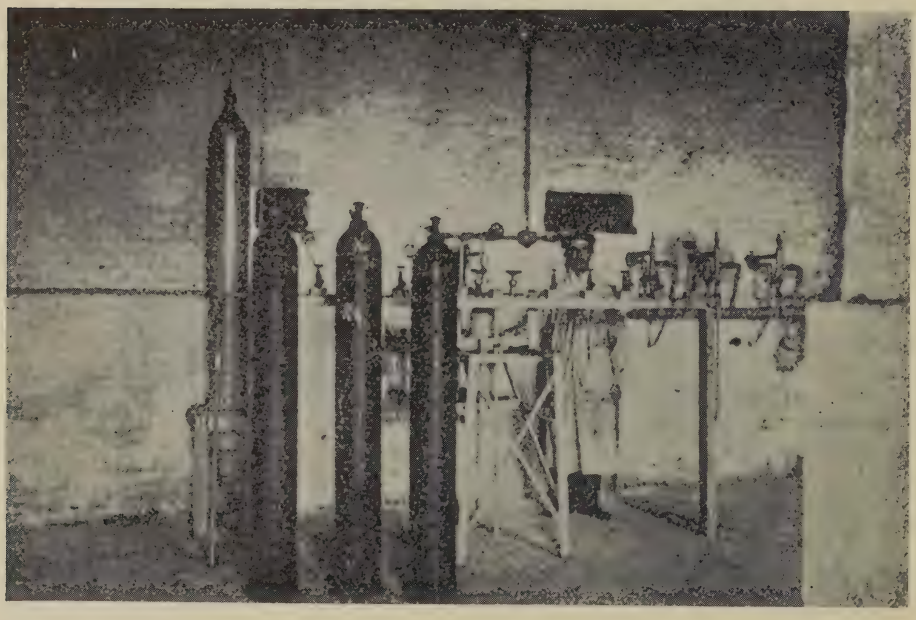


Fig. 8. Apparatus for producing high-pressure hydrogen.

production again, but as a result of the formation of iron carbide its effectiveness gradually declined. The hydrogen produced was exceptionally pure (the impurities amounted to no more than hundredths of 1%) and it could be drawn off from the reaction vessel at pressures of 200–300 atm. In further work on this reaction we first directed our attention to the development of apparatuses considerably exceeding the scope of laboratory facilities. In a small factory in a Hanover suburb we erected a battery of three vessels of 40 l capacity each and produced hydrogen continuously, which we drew off into pressure cylinders at the production pressure of 200 atm. The illustrations that follow (Figs. 6, 7, 8) give some details of this installation which looks extremely primitive today, but could only be put together with difficulty at that time.

The pressure vessels which were heated from the outside and in which several charges were processed every day, were sealed at the base by a conical closure held in position by a heavy screw. A man-sized spanner was used to disengage this contraption to place a new iron charge in position.

In this plant, as in our laboratory, the high pressure installation was on principle operated in a room separate from the control room. Regulating of heating, observation of pressures, drawing off of gases, etc., occurred in a control room separated from the reaction vessels by a stout wall.

In 1913 we had arrived at a method of working which permitted high pressure reactions to be conducted in apparatuses of 40–50 l capacity.

Saponification of organic chlorine compounds

At about the same time I started, together with Kurt H. Meyer, experiments on the hydrolysis of difficultly saponifiable organic chlorine compounds, in particular the *conversion of chlorobenzene into phenols* with caustic soda solution. This reaction, which cannot be carried out under normal conditions, is successful, as we were able to show, if chlorobenzene is heated with caustic soda solution at temperatures of about 300°; apart from phenol, phenyl ether forms in the first reaction phase, which can be converted into phenol after prolonged treatment, so that the chlorobenzene can be converted into phenol practically completely. The process can be carried out in a few hours and provides a cheap method for producing phenol from benzene in conjunction with alkali electrolysis. It has been carried out on a large scale in the USA under exploitation of our patents which were confiscated during the war, and continues to be used successfully there.

This reaction of course requires the use of the rotatable autoclave, to achieve thorough mixing.

Mention should be made in discussing this work of the conversion of ethylene chloride into ethylene glycol by treatment of ethylene chloride with bicarbonate solutions; these investigations were also made in 1913 and 1914. As was discovered at a later date, this reaction proceeded at a temperature which corresponded to a pressure of about 15 atm, so that high pressure methods were not strictly necessary in the later technical operation of glycol production.

Hardening of fats

As early as 1912 we worked on the problem of the hydrogenation of organic substances with the aid of highly compressed hydrogen. By virtue of the increased concentration of hydrogen at high pressure we hoped to achieve effects similar to those made possible at normal pressure by the action of catalysts. Special interest attached at that time to the hydrogenation of unsaturated vegetable and animal oils and fats. It was an obvious idea to study the hardening of fats with high pressure hydrogen, in particular with strongly unsaturated fats, such as the train oils. The results of treating such substances with high pressure hydrogen at about 300°, a temperature at which these oils in a reducing atmosphere can still be treated undecomposed, was, as the iodine numbers showed, a considerable decrease of the unsaturated character. It was however discovered that this phenomenon also occurred if treatment was carried out under the same conditions not with compressed hydrogen, but with compressed nitrogen. What was involved was, as could be established, a polymerization process. No addition of hydrogen at high pressure without catalysts to the unsaturated fractions of the fatty substances could be observed.

Oil hydrogenation

The action of highly compressed hydrogen in the treatment of heavy mineral oils was very different.

As early as 1910, Ludwig Landsberg had suggested that I should examine the problem of splitting heavy oils and oil residues into benzines. Experts were able to predict that the development of motor cars would lead to a

considerable increase in petrol consumption, although no one at that time had an accurate idea of the extent of this development. The cracking processes known at the time were extraordinarily imperfect. The losses that occurred in the cracking of oils in the form of coke, methane, and unsaturated hydrocarbons, were very high, and the formation of hard petroleum coke which separated on the walls of the cracking apparatus rendered the technical operation of the process difficult and expensive. After spending some time on this problem, I became convinced that the defects of the cracking processes and the poor quality of the unsaturated benzines produced could only be finally remedied *by ensuring that the hydrogen discharged during cracking in the form of methane was replaced by fresh supplies of hydrogen*, with the object of inhibiting the separation of hydrogen-deficient products leading to coking. It was to be expected that the benzines formed under such circumstances would have fairly saturated character.

Having obtained some data on the progress of the cracking reaction, we investigated the effect of highly compressed hydrogen on petroleum hydrocarbons under the temperature conditions at which the cracking reaction occurred. We attempted as it were to embed *the highly-compressed hydrogen in the molecular structure, loosened by high temperature, of the high-boiling petroleum fraction*. These experiments which were at first done in a vertical autoclave, clearly showed absorption of hydrogen by the cracking oils, non-occurrence of coke separation, and less unsaturated character of the lighter oils formed.

The application for the first patent on the *high pressure hydrogenation of oils* was filed in May 1913, some time after we had obtained experimental evidence of the practicability of the reaction. The delay in filing the application caused a lot of trouble later.

It was soon discovered that the temperature range in which the hydrogen had to be brought to react was narrowly restricted. It was important to work in a temperature range in which the velocity of the hydrogenation reaction was not excelled by that of the cracking reaction, and to keep the partial pressure of the hydrogen sufficiently high to ensure rapid progress of the hydrogenation reaction. At the same time care had to be taken to ensure that sufficient hydrogen was available to each splitting oil particle at all times. Naturally, this latter requirement could only be satisfied if sufficient mixing of oil and hydrogen was assured. It therefore represented a great step forward in the practicability of the oil hydrogenation reaction when we carried out this experiment in the rotary bomb mentioned above which permitted intimate mixing of gas and liquid.

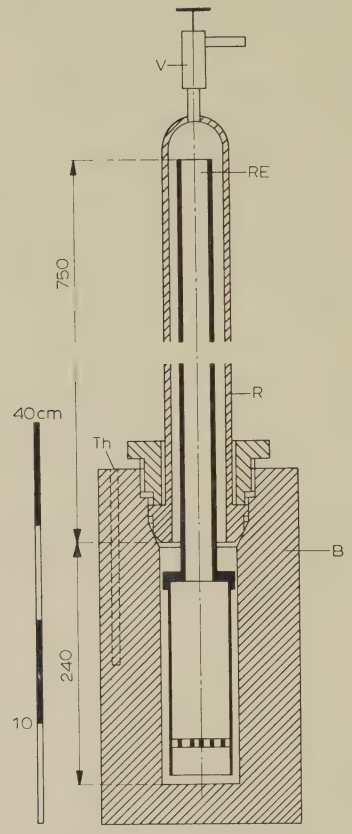


Fig. 9. Hydrogenation work. Vessel with insert, 1914.

Special experiments in which contact between the iron wall of the pressure bomb and the oil to be hydrogenated was prevented, proved that with oils the hydrogenation effect also occurs if any influence of the iron vessel walls is excluded, i.e. when metallic contact substances are prevented from participating (Fig. 9). The fact was however even then discovered and patented that addition of metals or metal oxides has a special effect in high pressure hydrogenation of oils, if the hydrogenation of sulphur-containing raw materials is involved.

It was soon discovered that the removal of the light products formed, and the supply of fresh hydrogen, had a very favourable effect on the process of the hydrogenation reaction. To put such operating conditions into effect, we had to use a fixed apparatus with agitator, because the rotary vessel did not permit continuous discharge of the substance (Fig. 10).

Work on the high-pressure hydrogenation of oils, in which Herr Paul Kalnin assisted me in a valuable way, had progressed sufficiently at the beginning of 1914 to enable us to work on a slightly larger scale, i.e. with the 40-litre reaction vessel which I have already shown you.

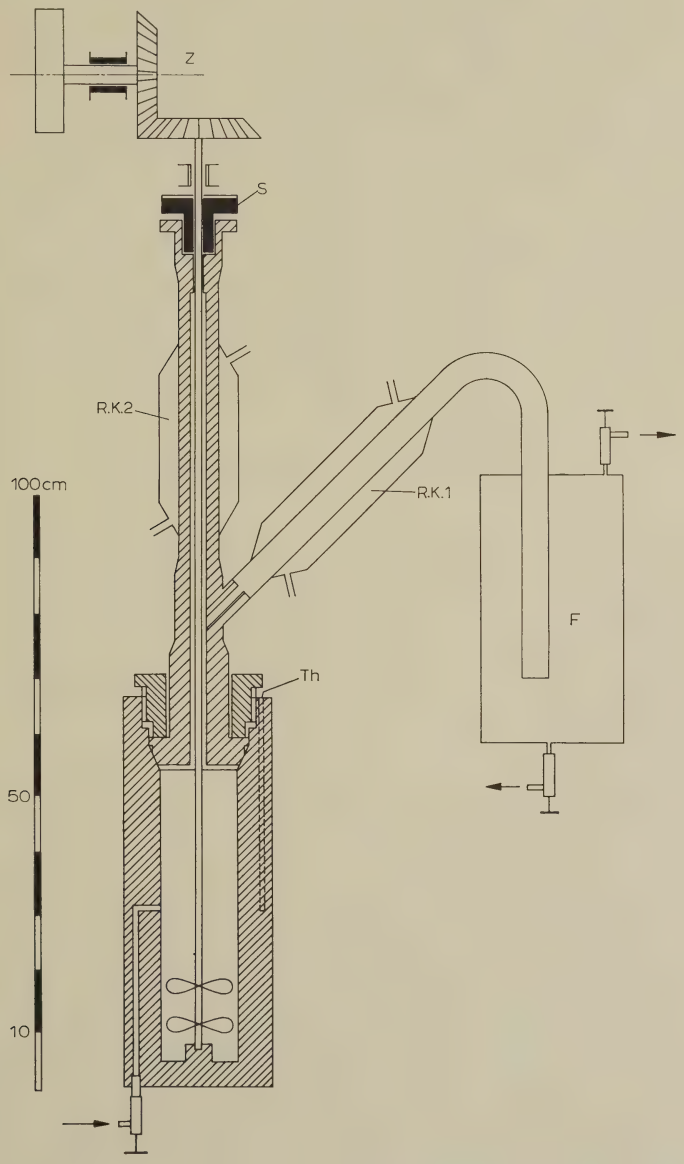


Fig. 10. Hydrogenation work. Vessel with agitator, 1914.

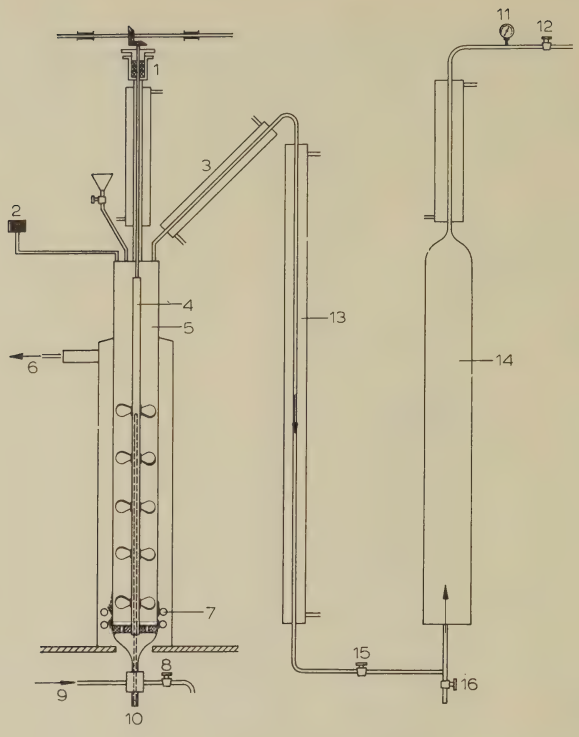


Fig. 11. 40-litre vessel with (vertical) agitator, 1914.

1 = stuffing box
2 = manometer
3 = reflux condenser
4 = agitator shaft
5 = decomposition vessel
6 = discharge
7 = heater
8 = discharge valve
9 = hydrogen supply pipe
10 = thermocouple
11 = manometer
12 = drain valve for unconsumed hydrogen
13 = cooler
14 = distillate cylinder
15 = throttle valve
16 = drain valve for distillate

Fig. 11 shows this somewhat more technical experimental apparatus. By contrast with later work, we used a vertical, externally heated, vessel into which hydrogen entered from below and bubbled through the liquid which was at the same time kept in motion by an agitator. The oil vapours flowed through a reflux condenser, in order to retain the heavy products which were then condensed under pressure in a conventional cooling system and collected in a distillation flask; excess hydrogen was discharged through a valve with small quantities of split gases. This step ensured discharge of the decomposed light products from the reaction space and renewal of hydrogen. A heavy

gas oil was processed at that time which was hydrogenated at a temperature of 430° and a pressure of 120 atm. About half the gas oil was converted into benzine without any formation of coke.

The investigations of the years 1913 and 1914 extended to the splitting of gas oils and distillation residues of crude oils from Galicia and Rumania. It was found that coke formation was avoided even when processing heavy residues by proper distribution of hydrogen, that the benzines formed had practically saturated character, that the sulphur in the oils was substantially separated as hydrogen sulphide, and that a further fraction of the sulphur was absorbed by added iron oxide, whereas the distillation products contained only slight amounts of sulphur.

The objects of our research were somewhat modified by the war in that the development of an industrial large-scale plant for the practical operation of hydrogenation came to the fore. This industrial work included hydrogenation of oil and coal; it will be discussed in more detail below.

Investigations into the origin of coal

I have already mentioned that we observed as early as 1911 in the treatment of peat in the presence of liquid water at temperatures above 300° that considerable quantities of carbon dioxide formed in this process, and that the composition of the powdery residue was close to that of natural fat coals. This observation prompted us to study this decomposition process of plant substances more closely because it might be similar to the process of metamorphism which these substances undergo in Nature in the course of millions of years during the gradual transition of vegetable substance into bituminous coal. Considerations of energy show that the principal constituent of plant substance, i.e. cellulose, which is formed by the influence of solar energy in the assimilation process and the subsequent reaction processes in the plant, is, thermodynamically speaking, an unstable substance whose rate of decay is however so slow at normal temperatures that the process escapes observation. Very large quantities of energy are liberated by cellulose decomposition, which is generally known from the processes of strongly exothermal carbonization of wood.

Very many researchers have attempted over the years to convert the plant substance, i.e. cellulose or wood, which contains apart from cellulose mainly the thermochemically similar lignin, into coal, by heating, i.e. by increasing

the rate of decomposition of cellulose, and when we began to examine the problem recent, elegant studies had been reported by Klason, Heidenstam, and Norlin, who had attempted to prevent the superheating of the carbonizing substance due to the heat of decomposition of cellulose, by introducing steam. In composition the carbonization products obtained by them approximate to natural coal, but their hydrogen content is still too low, because it was still impossible by the methods used to exclude overheating completely which leads to decomposition of the coal substance as it forms.

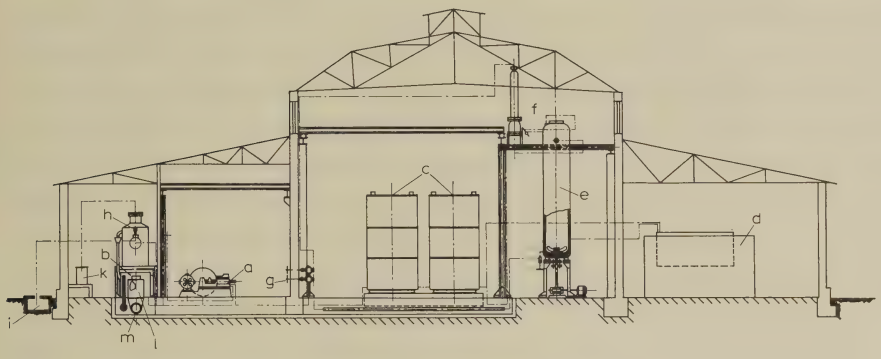
In our experiments, the carbonizing peat was in intimate contact with liquid water which was unable at the working temperature in the high pressure vessel to change to steam but absorbed and distributed the heat generated by the decomposition of the molecules, because it is a good conductor of heat. In the case under discussion, the water under high pressure served not as a reactant, but only as a heat-distributing medium, as it were a thermostat liquid.

With the same apparatus we carried out extensive and systematic experiments on the decomposition of the cellulose in wood and other plant substances at temperatures between 290 and 350°, in the presence of liquid water, i.e. at pressures of up to about 200 atm. The quantities of carbon dioxide and water formed were measured quantitatively. Per 2 parts cellulose, there were formed 2 parts carbon dioxide and 5 parts water, and a powdery substance which corresponded approximately to $C_{10}H_8O$. The hydrogen content fluctuated within narrow limits. If the hydrogen content of the solid substance was small, the gases contained slightly larger amounts of it. It would be devious to give details here about this reaction on which I worked for many years, at first with Hugo Specht and John Billwiller, and later with Paul Erasmus. In recent times, the reaction has reawakened the interest of chemists and has been studied in particular by Berl. I would like to mention that both cellulose and lignin, treated in this manner, lead to practically the same carbonaceous end products.

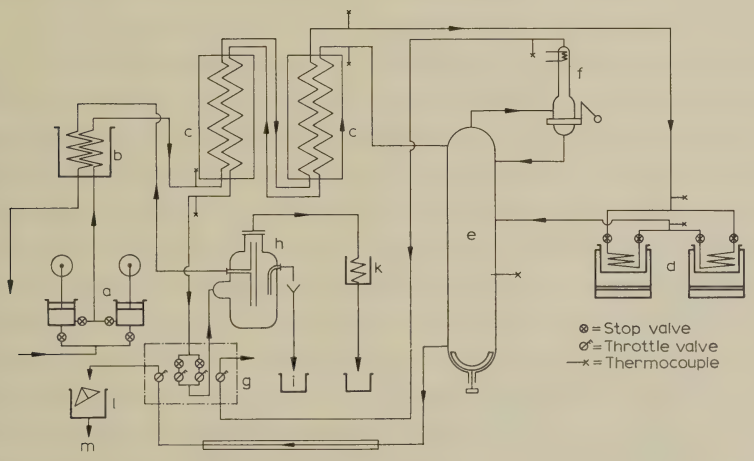
Coalification of cellulose effluents

The results of studies on the processes that occur during the decomposition of plant substance on heating in the presence of liquid water prompted Erik Hägglund and me to study the recovery of the effluents of the sodium and sulphate cellulose industry from the point of view of the coalification reaction. Nowadays, these effluents which contain lignin and other constituents

of wood that are soluble in alkaline media, are evaporated with expenditure of considerable quantities of coal, and the inorganic salts are liberated from the organic substances by combustion. It is known that highly offensive odours occur whenever the sulphate process is employed. We attempted to coalify the lignin dissolved in the effluents, i.e. to conduct separation of the organic substance from the aqueous solution under avoidance of evaporation by



(a)



(b)

Fig. 12. Diagram of cellulose effluent decarbonization.

a pump	*g* control post
b pre-heater	*h* tar separator
c heat exchanger	*i* tar receiver
d lead bath furnace	*k* cooler for alcohol vapour
e reaction vessel	*l* scales for coal slurry
f column	*m* screw conveyor

heating the effluents under pressure to about 300°. At this temperature the organic substance decomposes substantially into carbon dioxide and a readily separable coal-tar mixture. A little methyl alcohol also formed, and considerable quantities of acetic acid are found in the solution. Application of this process therefore avoids evaporation of very considerable quantities of water from the effluents. There is no need to burn the organic substance: it is largely recovered as coal and tar and there is moreover a fairly considerable yield of acetic acid.

The acetic acid obtained need not be isolated after each boiling process, because storing of acetic acid in the effluents is by no means disadvantageous for the cellulose boiling process. It is sufficient if after each boiling process about $\frac{1}{5}$ of the solution is concentrated to produce the acetic acid which is obtained in the form of sodium acetate. This process is likely to gain importance for the cellulose industry. Fig. 12 shows the experimental apparatus for the operation of effluent carbonization.

Hydrogenation of coal

The investigations into the conversion of cellulose into coal by coalification in conjunction with our studies on the hydrogenation of heavy oils opened the way to the discovery of the *process for liquefying coal*. We had observed that a product forms from cellulose with splitting of certain quantities of carbon dioxide and water which we considered to be similar to natural coal, and we had further observed that the hydrogen in this so-called synthetic coal is unstable. The attempt to formulate this process of cellulose decomposition led me to a hypothetical concept of the constitution of this coal-like substance formed from cellulose. I assumed that our artificial coal is a compound of carbon, hydrogen, and oxygen – that coal is not carbon, was not obvious at the time – whose structure must resemble that of certain unsaturated compounds of terpene-like character, and that this compound should be capable of absorbing not inconsiderable quantities of hydrogen. By hydrogen absorption, such a compound would approach the class of heavy petroleum hydrocarbons. As a consequence of these trains of thought of whose hypothetical character I have always been aware, it was an obvious step to attempt hydrogen addition to coal and to endeavour at the same time to discover whether the hydrogen-charged coal can be split into medium and light hydrocarbons. This experiment was done analogously with the oil hydrogenation tests at

my suggestion by my assistant Hugo Specht in the summer of 1913, and *even the first test showed that 80% of a coal obtained by cellulose coalification passed on treatment with hydrogen at about 150 atm pressure and at temperatures between 400 and 450°, into gaseous, liquid and benzene-soluble substances.*

On being repeated with natural coal these experiments gave practically the same results. They became the basis of the process for the production of liquid and soluble compounds from coal, i.e. of the process which we soon called « *coal liquefaction* » and for which I filed a patent application in the autumn of 1913.

It was soon discovered in the course of the experiments that the addition of hydrogen to the coal substance resulted in not inconsiderable evolution of heat. We prevented the noxious, decomposing effect of this heat by hydrogenating the coal in suspension with a suitable oil which was liquid at the operating temperature. The added oil had practically the same effect as the water added during coalification. It absorbs the heat occurring at the site of the reaction, distributes it, and by this means avoids local overheating. Once again it is mainly a heat distributing liquid, although at the same time it undergoes splitting at high temperature under the effect of the hydrogen.

The first experiments with coal hydrogenation were carried out, similarly as the experiments with oil, in our small vertical experimental pressure vessel; further development was carried out in the rotary vessels which made for good penetration of the reacting material by hydrogen. Soon after the discovery of this reaction it was found that all so-called younger coals are more or less suitable for the process, both brown coals and bituminous coals, and that wood and lignin could of course also be liquefied, particularly after previous coalification. Not amenable to the hydrogenation reaction were the hydrogen-deficient and anthracite coals, whose carbon content in the ash-free substance exceeds 85%. This observation was in agreement with the view we had formed from certain results of earlier coalification experiments. It was found that the addition of metal oxides, in particular iron oxides, has a favourable effect on the hydrogenation of coal also. We attributed this effect to the prevention of polymerization of the heavy fractions, brought about by the sulphur present.

During hydrogenation, a certain amount of gas forms; a considerable amount of carbon dioxide in young brown coals: little of this is formed in bituminous coals. Methane and some ethane always form, and about half the oxygen present in the bituminous coal is found as water in the reaction product. The nitrogen is found in the distillation product in the form of

ammonia and nitrogen bases, most of the sulphur escapes as hydrogen sulphide. Most of the carbon is present as light, medium, and heavy oil, a carbon residue goes to waste as hydrogen- and oxygen-deficient compound with the ash as non-liquefied substance. This fraction of non-liquefied carbon depends on the nature of the coal used. In brown coals it is extraordinarily small, in the best case no more than 1%, in coals with a high fusain content it rises to 20% and more.

Circumstances did not permit us to carry out systematic investigations, either in oil or coal hydrogenation, into the effect of catalysts on increased absorption of hydrogen by the cleavage products of the basic substance. Scattered observations had shown as early as 1920 and 1921 that detailed investigations into this subject would be promising, but we lacked experience, experimental apparatus, and staff for carrying out such investigations effectively. We had to content ourselves with developing the hydrogenation processes in the manner in which they can be operated in the direct process without subsequent catalytic treatment.

Industrial high-pressure apparatus

Sufficient light had been thrown in 1914 on the hydrogenation reaction of heavy oils and coal with the assistance of Messrs. Specht, Kalnin, Billwiller, to permit deliberation as to whether and how industrial apparatus for the operation of these reactions on a large-scale could be erected. Industrial high-pressure apparatuses had at that time only been built for gas reactions in the homogeneous system. It was our task to construct apparatuses in which liquids, solids, and gases could be introduced, heated, mixed, and made to react, and from which the reaction products could be continuously discharged. Industrial apparatus for the hydrogenation of coal and oil was developed during the years 1915–1925 in our Mannheim-Rheinau factory particularly with the assistance of Messrs. Tillmann, Debo, Prof. Riedler and Löffler.

Since temperature and pressure conditions are practically the same for the hydrogenation of heavy oils and coal, and considering that intimate contact between the hydrogen and the liquid or suspension to be hydrogenated is essential in both reactions, it could be assumed from the beginning that an apparatus suitable for oil hydrogenation could, suitably supplemented, be applied to the liquefaction of coal. In both processes it was necessary to introduce *solid substances* into the reaction apparatus – relatively small quantities

of iron oxide for desulphurization in oil hydrogenation, the entire raw material in coal hydrogenation. It was obvious from the start that the introduction of solids into a high-pressure reaction chamber and the discharge of solid residues would present special difficulties, and it took several years before a suitable solution of this technical problem was discovered.

Suitable reaction apparatuses were cylindrical, forged or pressed steel vessels which could at that time, in 1915, be fabricated with a diameter of about 80 cm. Because of this restriction on the diameter, cylinders of considerable lengths had to be used to get a reaction chamber of significant size. We decided to use a vessel 8 m long. The fundamental question was if these cylinders should be arranged vertically or horizontally. With the vertical arrangement, the reaction had to be conducted in a relatively high column of liquid, through which the reaction gas flowed and to which it imparted turbulence. Provided the quantity of flowing gas was sufficient, it appeared feasible to work without an agitator and to leave the hydrogen to perform the task of mixing or agitation. In this arrangement it had to be accepted that during agitation the newly supplied reaction material constantly mixed with the as yet unprocessed material, and that the residue drawn off always contained still unprocessed or only partly hydrogenated material. We therefore decided to use a horizontal vessel with agitation, which the raw material entered at one end, while the hydrogenated products were drawn off at the opposite end. Hydrogen and oil were heated before entering the vessel approximately to the reaction temperature, to make maximum use of the expensive reaction space. Since, at the operating temperatures, the strength of iron is considerably

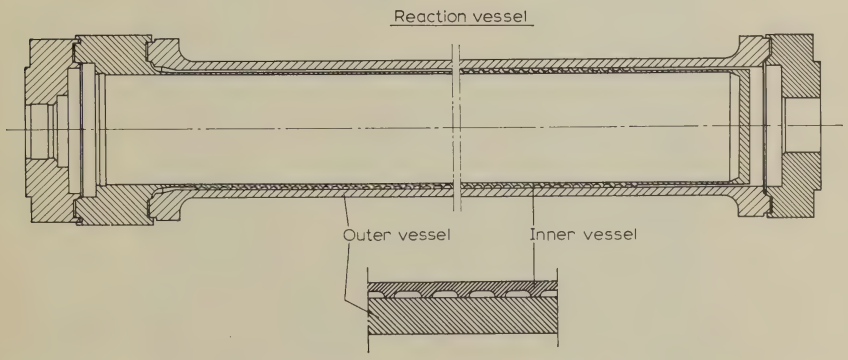


Fig. 13. Bergin plant Rheinau of the Deutsche Bergin AG für Kohle und Erdölchemie, Mannheim-Rheinau.

below the maximum strength attained at 300°, we decided from the start to dispense with heating of the pressure vessel from outside, because any external heating would have meant that the iron was brought to temperatures higher than the maximum temperatures necessarily required for the reaction. Heating was effected inside the pressure vessel in that into the pressure vessel there was built a second relatively thin-walled pipe (Fig. 13). Heating medium practically at the same pressure as that prevailing in the reaction space was pumped through the narrow space between the two pipes.

Originally, the heating medium selected was naphthalene, the only liquid substance which withstood the temperature required for any length of time. Difficulties in operation arose because of the position of the melting point of naphthalene, and we therefore later used a compressed gas (nitrogen or combustion gases) as heat carrier, which method of heating proved highly successful.

The heating gas was pumped by a high-pressure circulating pump in the manner (Fig. 14) such that it passed from the pump in the cold state first through a double-coil system in which the vapours issuing from the vessel

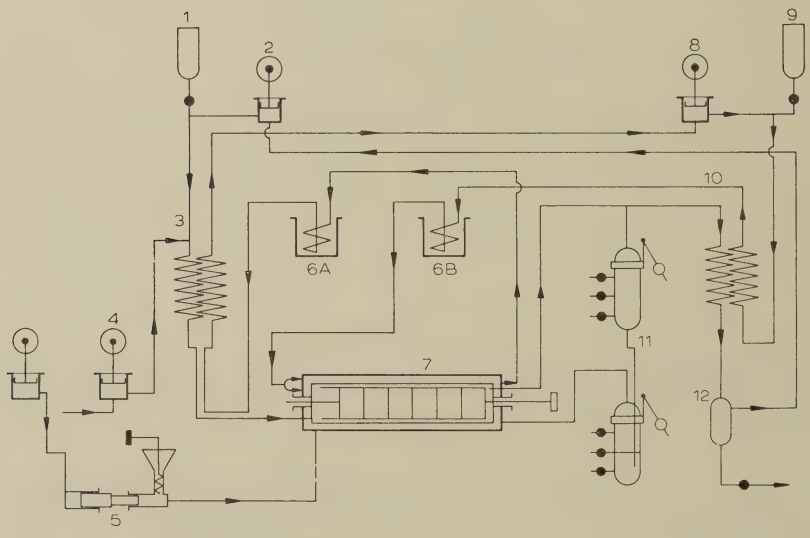


Fig. 14. Diagram of high-pressure apparatus.

1 = hydrogen cylinder
2 = hydrogen pump
3 = heating system
4 = pump
5 = paste press
6 = heating furnaces (A and B)
7 = reaction vessel
8 = heating medium pump
9 = heating medium container
10 = condenser
11 = equalizers
12 = collectors

condensed. In this manner, it was heated to above 300°. It was then heated in a furnace, passed through the jacket space of the vessel into a second heating furnace and then to a further double-coil system where it generated the heat for heating the hydrogen and the oil. The cooled heating gas returned to the pump. In this way good thermal economy and readily controllable heating was ensured. The temperature in the reaction chamber could be held constant within a few degrees for weeks at a time. The products discharged from the condensers were collected in high-pressure vessels.

The more rapidly the products formed are removed from the reaction system, the better the cleavage reaction progresses. Hydrogen was therefore used in excess. It had to be kept in circulation. It left the reaction vessel together with the vaporous and liquid products, was cooled and separated in the product-collecting vessels from the condensable oils and from most of

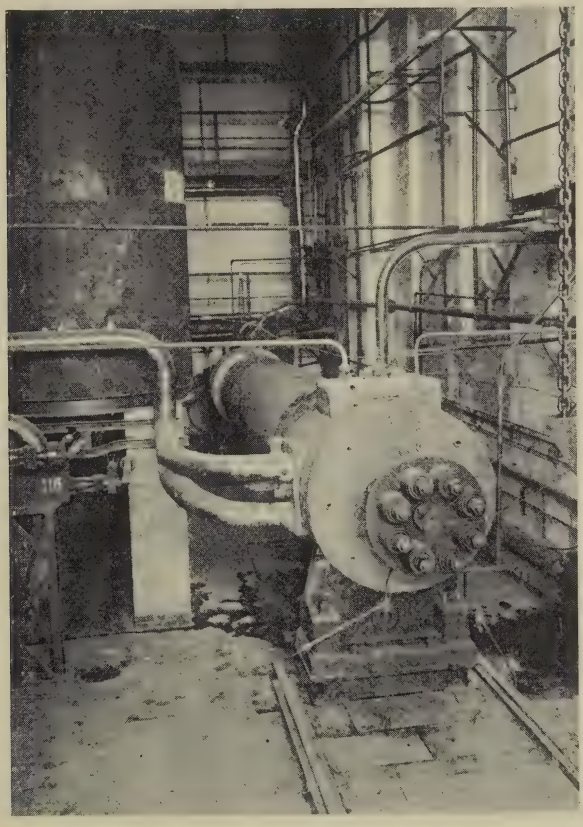


Fig. 15. High-pressure vessel.

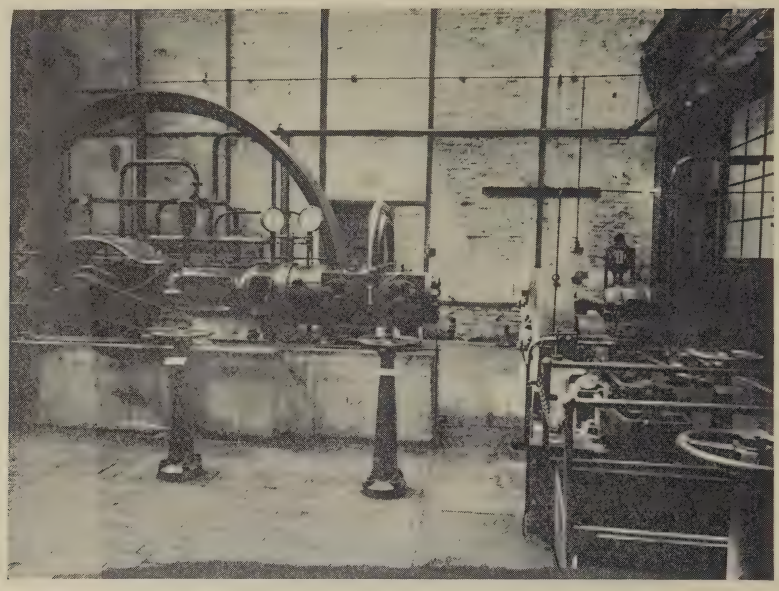


Fig. 16. Circulating pump for compressed nitrogen.

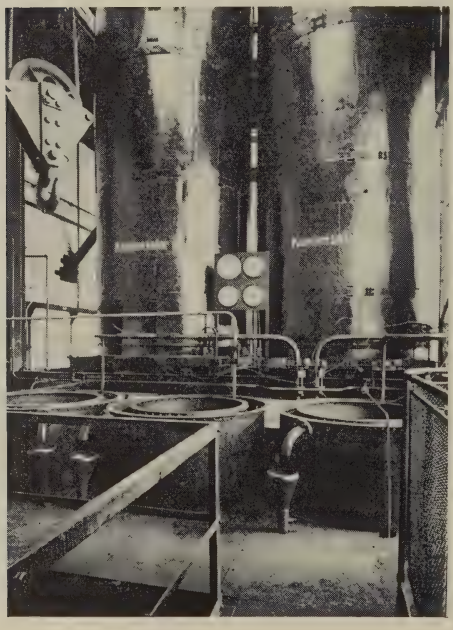


Fig. 17. Condensers.

Fig. 18. Collecting tanks for finished products.

Fig. 19. Control post and measuring instruments.

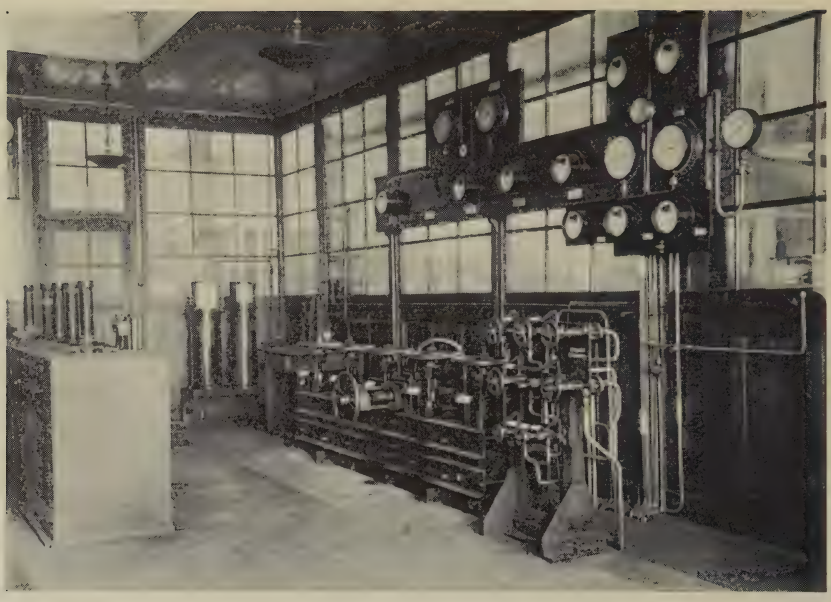


Fig. 20. Control post and measuring instruments.

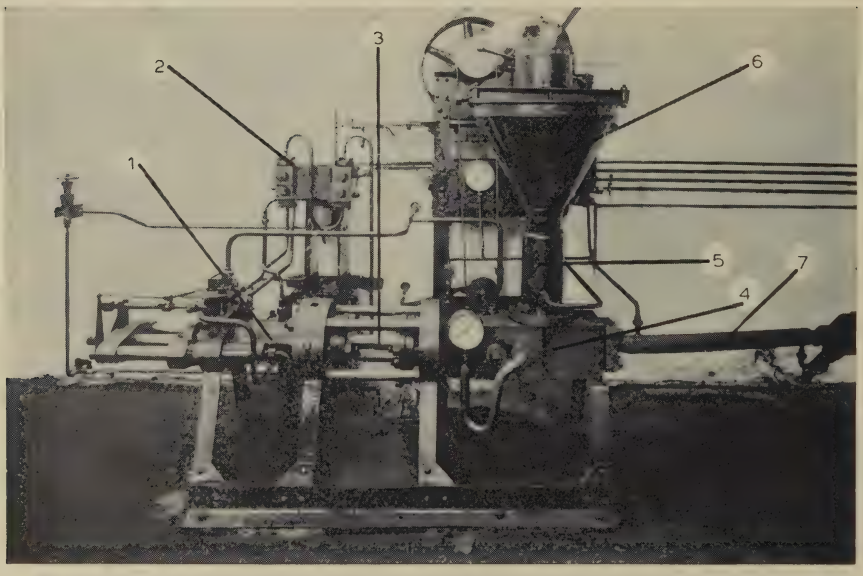


Fig. 21. Paste press for coal feed.

1 = hydraulic cylinder
2 = reversing valve for 1
3 = piston rod
4 = cylinder for the paste
5 = screw conveyor
6 = filling funnel
7 = transport pipe

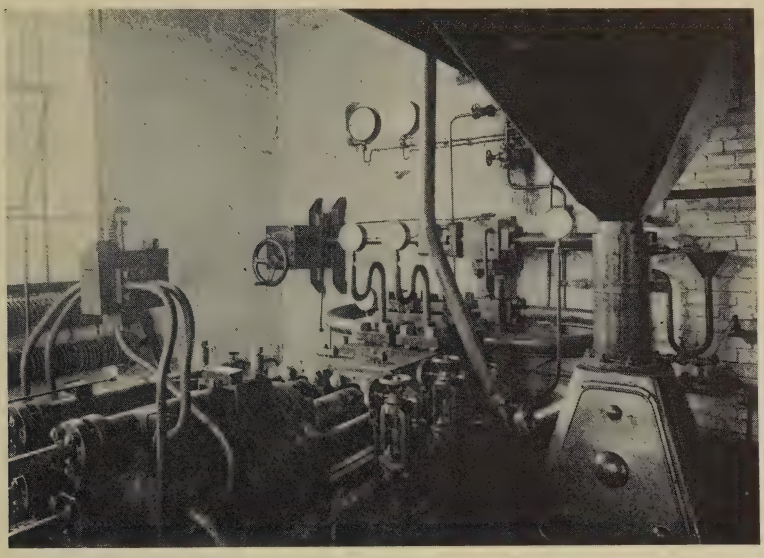


Fig. 22. Paste press for coal feed.

Fig. 23. Test rig for small-scale experiments.

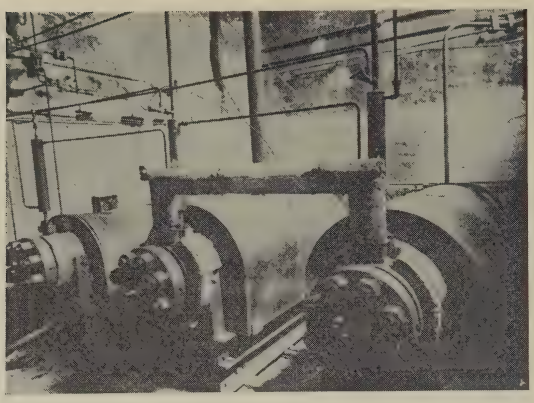


Fig. 24. Reaction vessels of continuous experimental plant.

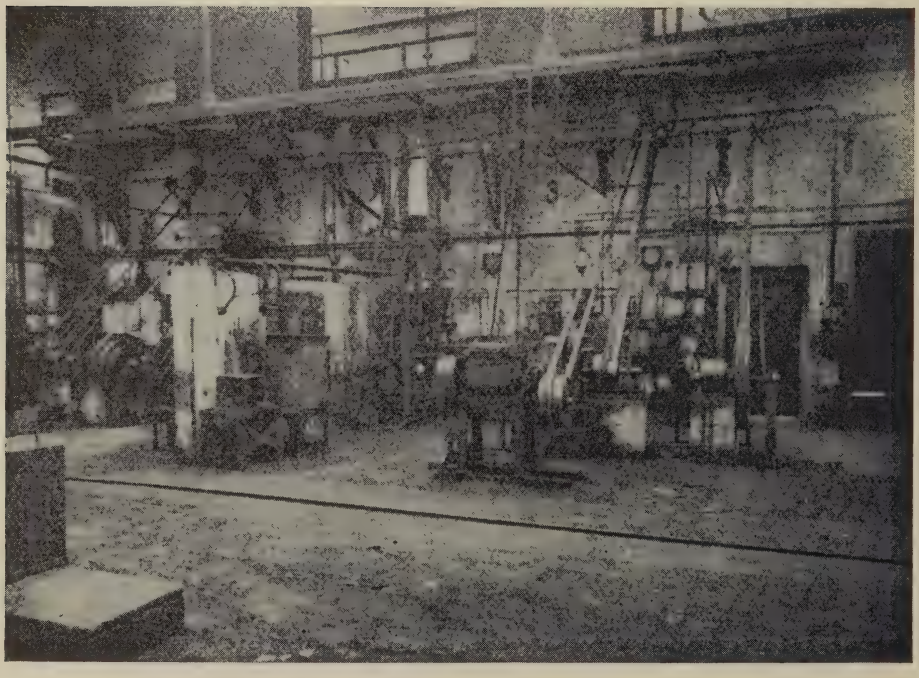


Fig. 25. Machine-room for continuous experimental plant.

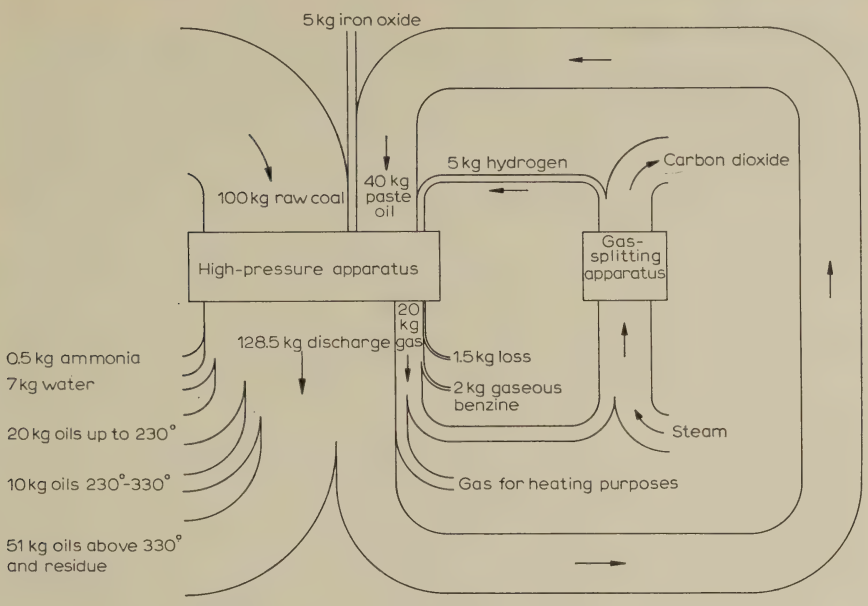


Fig. 26. Flow diagram of continuous method of operation.

the methane which is readily soluble in oil, and was returned to the vessel by a circulating pump. Following various modifications, this arrangement proved very suitable.

Construction work began in 1915, and the apparatus had reached its final form about 1924. Figs. 15–20 show parts of the apparatus.

The design of reliable stuffing boxes for carrying the agitator shaft into the vessel presented great difficulty at first. The construction of an agitator 8 m long was also far from simple. New instruments had to be developed for measuring the flowing high-pressure gases. The design of durable valves which regulated the expansion of the reaction products consisting of liquid, solid, and gaseous substances from 150 atm to 1 atm presented great difficulty, but was accomplished satisfactorily. To feed solid coal as simply as possible continuously to the high-pressure space presented particular difficulty. A suitable method for doing this was found in 1920. The coal was mixed with highly viscous oil, e.g. tar or the heavy fraction of the product formed in coal liquefaction, into paste that was stiff at normal temperatures and which could be circulated by hydraulically-operated pistons with the assistance of a specially designed pump. (Fig. 21 shows the paste press of the small, Fig. 22 that of the large apparatus.)

In our large experimental apparatus at Mannheim-Rheinau, construction of which commenced in 1916 and which started experimental operation in 1919, we studied mainly the splitting of oil residues on a large scale. Heavy sulphur-containing products, such as the residues of Panuco oils, Persian oil residues, and other products were processed. The maximum daily output was 30 ton. Depending on the starting material, we obtained

25–35% benzine,
40–50% gas oil,

the remainder being heavy products which could be processed to lubricating oils. The waste products were a small percentage asphalt and a few percent methane.

When the large-scale apparatus had been sufficiently tested with oil, it was at the end used for a short period for processing coal.

The study of coal liquefaction was mainly conducted in smaller experimental plants. Preliminary tests, several thousand of them, were carried out in a rotary vessel apparatus (Fig. 23). About 200 different types of coal were investigated in this manner, mainly in the years 1922–1925. For more extensive investigations we used apparatus with a continuous throughput of about 1 ton per day which operated on the same principle as the large-scale apparatus, except that the method of heating it was simpler. Experimental work was successfully conducted at that time by Messrs. Noack, Hofsäss, Schoenemann, Rheinfelder. Figs. 24–25 show the experimental rig.

The diagram, Fig. 26, shows the results of liquefying a normal bituminous coal: 100 parts coal are mixed with 40 parts oil, taken from the process, with addition of a little iron oxide, and are introduced into the high-pressure apparatus in the form of a paste with 5 kg hydrogen. About 128 kg liquid and solid products and 20 kg gas are obtained. About 7 kg water are separated from the discharge; the water contains about $\frac{1}{2}$ kg ammonia.

The following are obtained from the oil:

20 kg products with a boiling point up to 230°
10 kg products boiling between 230 and 330°, and
51 kg heavy oils and asphalt,

in which are contained the inorganic constituents of the coal and the non-liquid or soluble coal substance, amounting, in the case under discussion, to about 10% of the coal used. These products and about 2 kg benzine which are recovered from the gas represent the yield from the coal used.

Corresponding to the 40 kg paste oil supplied, an analogous fraction must be returned to the process. The experimental apparatus permitted operation with a degree of accuracy such that at a daily throughput of 1 ton coal, the products introduced were recovered in the end products except for a loss of about 1%.

As a rule, the processing of brown coals or pitch coals presented less difficulty than did bituminous coal and produced higher yields. I have already mentioned that we were able to open up the ash-free substance of such coals except for a residue of about 1%.

On average, hydrogen consumption amounted to 5% of the weight of the coal. No difficulty arose in causing considerably larger quantities of hydrogen to be taken up by further pressure treatment of the primary products, which greatly increased the yield of low-boiling products at the expense of the high-boiling oils. Economical considerations will decide the extent to which hydrogen consumption may be increased in hydrogenation of coal and its liquefaction product.

From the gaseous products, methane and ethane, hydrogen and carbon dioxide can be produced by splitting at high temperature in the presence of steam, employing a process to whose industrial development we successfully applied ourselves for some time. The reaction proceeds in two stages. Methane and steam are converted into carbon monoxide and hydrogen

$$CH_4 + H_2O = CO + 3H_2.$$

Further hydrogen forms by passing the mixture of carbon monoxide and steam over a catalyst in the presence of excess steam

$$CO + H_2O = CO_2 + H_2$$

so that, according to the formula

$$CH_4 + 2H_2O = CO_2 + 4H_2$$

four molecules hydrogen are formed for each molecule CH_4. It is sufficient to split part of the methane–ethane mixture in this way to obtain the quantity of hydrogen required for the process. The carbon dioxide mixed with the hydrogen can easily be separated with water under pressure following the compression of the gases. As far as I know, this principle of hydrogen production is now being exploited in America for the hydrogenation of oil.

The separation of the heavy oil fractions from the inorganic substances presented major problems. Since this point is of essential importance for the

practical operation of coal liquefaction, we examined it in detail and found separation could satisfactorily be accomplished by filtering the discharges in filter cells at suitable temperatures. We discovered that the more completely the product issuing from the apparatus had been subjected to the action of hydrogen, the more easily separation could be effected. Complete hydrogenation can be achieved in a horizontal vessel if the agitator is so designed as to prevent mixing of unprocessed and semi-finished products with the finished product, which is not possible in vertical hydrogenation apparatus. Oils with good lubricating characteristics were recovered from the heavy fractions of the coal oil.

As already mentioned, we carried out no systematic investigations into the influence of catalysts on the hydrogenation of heavy oils and coal. The elegant investigations into the effect of various catalysts on these hydrogenation processes at the Badische Anilin- & Sodafabrik were carried out when our own researches were nearing conclusion, and these investigations resulted in the hydrogenation processes now being operated at the factories of I.G. Farbenindustrie.

My own work on high pressure has now come to an end. Many problems which stimulated the urge to research in the course of work on high-pressure reactions which lasted for almost two decades, must remain uninvestigated, because efforts are now devoted to another field. The need for concentration is an important result of many years of practical research.

Biography

Friedrich Bergius was born on October 11, 1884, in Goldschmieden near Breslau, Silesia. He belonged to an old respected family of scientists, theologians, civil servants, army officers, and business men. His grandfather was Professor of Economics in Breslau and his father owned a chemical factory in Goldschmieden.

Bergius was educated in Breslau and whilst still at school took great interest in his father's factory where he was able to study various working methods under the guidance of his father and thus became acquainted with chemico-technical processes. The time spent in the laboratories and the works there later stood him in good stead, as already at a very early age he obtained considerable insight into industrial as well as scientific matters.

Before entering University, Bergius was sent to the Ruhr for six months by his father, where he studied the practical aspects of a large metallurgical plant and profited greatly by this experience.

In 1903 he entered Breslau University to read chemistry under Ladenburg, Abegg and Herz; after doing one year's military service he proceeded to Leipzig University in 1905 and worked under Hantzsch on his thesis *Über absolute Schwefelsäure als Lösungsmittel* (On absolute sulphuric acid as a solvent). This work was completed in Breslau under Abegg, and Bergius received his degree at Leipzig in 1907. The lively scientific atmosphere in the laboratories of Hantzsch and Abegg induced Bergius to devote himself to a career in scientific research; for this reason he worked for two further terms at Nernst's Institute in Berlin and then went to Karlsruhe to study under Haber for one term in 1909.

The work which was being carried out there on the chemical equilibrium in gas reactions, in particular that on the synthesis of ammonia, prompted his own research in Hanover in 1909. He started with a detailed investigation on the dissociation of calcium peroxide and developed a practical method for laboratory work at pressures up to 300 atmospheres.

The equipment available in the laboratories of the Technische Hochschule in Hanover soon proved insufficient and in 1910 Bergius established his own

private laboratory in Hanover, which was gradually extended by several workshops and plants, and where he employed a number of collaborators. The most important result of his research was the hydrogenating effect of hydrogen on coal and heavy oils under high pressure, in 1912 and 1913.

It was not easy to obtain the means for maintaining this laboratory, especially as the scale of the experiments had to be enlarged in order to apply the laboratory methods to a small industrial scale. Therefore in 1914 Bergius accepted an offer made already previously by Dr. Karl Goldschmidt to transfer his laboratory to the Essen works of the firm Th. Goldschmidt A.G.; shortly afterwards he also accepted an executive position in this firm.

For a short time in 1911 Bergius lectured on technical gas reactions, equilibrium theory, and metallurgy at the Technische Hochschule in Hanover. However, the outbreak of the First World War and the increased rate of work on the problem of liquefaction of coal made it impossible for him to continue with his teaching activity. From 1914 to 1921 he lived in Berlin.

A comparatively large industrial plant for the technical development of the hydrogenating process was set up in Rheinau near Mannheim. It was soon found that the scope of this research work was too large for one firm alone and after the end of the war Bergius endeavoured to find firms suitable for collaborating in the development of hydrogenation. Apart from groups of German companies, he also induced the Shell Trust and a number of British enterprises, in particular the coal industry, to collaborate with him. However, in critical times he still had to bear the whole responsibility and risk for the further development of the process. Finally, in 1927, he was able to conclude his own work on the liquefaction of coal, after the practical possibilities had been proved on a large scale. The I.G. Farbenindustrie and Imperial Chemical Industries then took up the work on an industrial scale.

From that time onwards Bergius devoted himself to a process of obtaining sugar from cellulose in wood, on which he had already worked during the First World War. He succeeded after 15 years' work and an industrial plant was set up, also in the Rheinau works. It is amazing with what intensity Bergius took up the second part of his life's work, namely this hydrolysis of cellulose in wood and similar substances to sugar. It seems as if the well-known difficulties of working with highly concentrated hydrochloric acid had presented a special challenge to Bergius. Initially the process was taken up only in England and only during the thirties did Bergius manage to continue these experiments in Germany; his main concern was to rationalize the process and to ensure complete recovery of the hydrochloric acid used by

constructing intricate devices. In 1921 he moved to Heidelberg, in order to be near his technical work in Mannheim-Rheinau, and at the same time to be in contact with Heidelberg University.

His home was international, and always full of mentally alive people. He had done great work and had received most of the honours possible during the eventful epoch of his lifetime. He received the degree of Dr. Phil. from the University of Heidelberg and the honorary doctorate from the University of Hanover; he was awarded the Liebig Medal and was elected to the Board of Directors of many associations and companies interested in coal and oil. In 1931 he shared the Nobel Prize with Carl Bosch for their contributions to the invention and development of chemical high-pressure methods.

After the last war it was impossible for Bergius to find a field of work in Germany which would have done justice to his abilities. He emigrated to the Argentine, where death put an end to his eventful career in Buenos Aires in 1949.

Chemistry 1932

IRVING LANGMUIR

«for his discoveries and investigations in surface chemistry»

Chemistry 1932

Presentation Speech by Professor H. G. Söderbaum, Chairman of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

Superficiality is a quality which has always had a bad reputation, not least within the field of science and among scientific practitioners. In these circumstances it may possibly arouse some surprise that, in awarding this year's Nobel Prize for Chemistry, the choice of the Royal Academy of Sciences has fallen on a work on surface chemistry. But here, as often in other cases, it is necessary not to let words obtain too great a power over thought. If one frees oneself of this power and investigates the matter more closely, it will be found, on the contrary, that in reality surface chemistry has contributed greatly to the deepening of our knowledge of matter in its most minute particles.

Surface chemistry as the designation of a special discipline within physical chemistry is a comparatively new conception. The phenomena with which it is concerned are none the less well-known since of old.

One of these phenomena is that of adsorption. The power of certain solid bodies to retain or, as we say, to condense gases on their surface has long been known and made use of for all manner of practical purposes. But it has not been known how this adsorption really takes place – and opinions have been divided as to what forces operate thereby. As a rule the conception will probably have been that the gas nearest to the adsorbing solid body, thus in the boundary surface between the solid and the gaseous condition itself, appears in a more or less condensed state, and that the density decreases continuously outwards in proportion as the solid surface is left, in about the same way as the density of the atmosphere of the earth decreases upwards in proportion as we move away from the solid crust of the earth. This year's Nobel Prize winner in Chemistry has advanced an entirely conflicting theory and one which at first sight seems to be particularly bold.

According to this theory the layer of gas adsorbed is limited – in ideal border-line cases at least – to an extremely thin film of gas molecules extending over a single plane, thus a film whose thickness is that of a single molecule or, in other words, is monomolecular. And the force which retains

the gas particles is derived from the chemical field of forces of the surface atoms, in that the atoms on the boundary surface are conceived as partially unsaturated and, in virtue of their so-called residual valences directed outwards, equipped with the power to bind a corresponding number of atoms in the gaseous body. And since these residual valences – in any case in crystalline bodies – must be conceived to make their effects felt at fixed points and at fixed distances from each other, it follows immediately that the adsorbed gas particles also will lie at fixed distances from each other and at fixed points. One can visualize it most easily if one thinks of the adsorbing solid surface as a chess-board, where each square can only be occupied by a single gas particle. When all the squares are occupied adsorption ceases.

Now it may be asked: Is there any real basis for such an assumption? Can one really adduce in proof anything which seems so to escape direct observation? With the view of answering these questions I will venture to borrow an example from an account sent in to the Academy of the work which has been awarded the prize.

Assume that hydrogen gas is exposed at very low pressure in an electric bulb to the influence of the hot metal filament. The hydrogen gas molecules are broken up, dissociated into atoms, and these are strongly adsorbed by the glass surface of the wall of the lamp, if the latter is kept well-cooled with liquid air. One finds then that a maximum quantity of hydrogen is taken up by the glass surface, or by a certain part of it, let us say one square centimetre. On the other hand, the size of the hydrogen atoms is known, and so the number of atoms which ought to find room on the same surface unit can be calculated. It is then shown that the quantity of hydrogen gas thus calculated is in satisfactory agreement with that previously found. The layer of hydrogen gas is thus, approximately at least, only of the thickness of one layer of atoms.

Another experimenter has allowed a known surface of metallic gold to adsorb air during the transition from a very high vacuum to ordinary atmospheric pressure. With the help of an extremely sensitive micro-balance he has been able to make a direct determination of the amount of air thus retained by the gold and found that it corresponds to a layer of oxygen and nitrogen molecules of only the thickness of one molecule.

Quite new methods of determination, based on the use of electron bombardments and the determinations of electron interferences, have finally indicated that when, for example, hydrogen is adsorbed on the surface of a nickel crystal, a regular pattern is formed, where the distance between the

atoms of hydrogen is twice as great as the distance between the atoms of nickel. Thus, a pretty confirmation of the conception of the adsorbing surface as a chess-board, where the adsorbing particles are retained in definite positions.

The work which has been awarded the prize does not, however, comprise only investigations concerning the adsorption in the boundary surface between gases and solid bodies, but also investigations concerning the thin films in the boundary surface between gases and liquids and concerning the adsorption on the surfaces of liquids. The well-known phenomenon of the spreading of an oil film has served as a starting-point for these investigations and the determination of the lateral pressure with which such a film opposes attempts to diminish its surface.

It has been found *inter alia* that there are such films where the molecules can move around each other freely, something like the molecules in a gas, but with the difference that here they only move in two dimensions, while in an ordinary gas they move in three. This has opened a new and important field for investigations in chemistry: the study of the conditions of matter in the two-dimensional world, and has in addition afforded valuable information, not only as to the structure of molecules, but also as to the forces working within and between them.

In the rules of the Nobel Foundation we read: «No work shall have a prize awarded to it, unless it has been proved by the test of experience or by the examination of experts to possess the pre-eminent excellence that is manifestly signified by the terms of the will.»

In this respect, if at first there could have been any uncertainty as regards the work now awarded the prize, this uncertainty has been ever increasingly dispelled in the light of the researches of the last few years, to be succeeded by an increasing insight into the fact that the work breaks entirely new ground and that considerable parts of it are of lasting value.

This value appears in a still clearer light if we reflect that a multitude of chemical reactions of the utmost importance both technically and biologically, not to mention physiologically, are precisely surface reactions and consequently cannot be fully comprehended or mastered without an intimate knowledge of the nature of the elementary surface processes.

Numerous scientists are at the present time working industriously and successfully in this field of research. It would seem, however, that greater honour is due to the first man, the pioneer, who has broken new ground, than to the cultivators of ground already cleared, however industrious they may be.

Influenced by these considerations the Royal Academy of Sciences has decided to award this year's Nobel Prize for Chemistry to Dr. Irving Langmuir of Schenectady « for his outstanding discoveries and investigations within the field of surface chemistry ».

The Royal Swedish Academy of Sciences is sure that it is acting in accordance with the views of the scientific world in awarding to you this year's Nobel Prize for Chemistry for your most important discoveries and researches in the field of surface chemistry.

In proffering to you the sincere congratulations of our Academy, I have the honour of asking you to receive this prize from the hands of His Majesty the King, who has been graciously pleased to undertake to present it to you.

Irving Langmuir

Surface chemistry*

Nobel Lecture, December 14, 1932

The phenomenon of adsorption has been known and has been studied for many years. For example, Sir James Dewar found that charcoal cooled in liquid air was capable of taking up large quantities of such gases as oxygen and nitrogen. This was known to be a surface action depending on the very fine state of division of the charcoal.

The effect of soap in lowering the surface tension of water depends upon the presence of a higher concentration of soap molecules in the surface layer than in the solution.

Willard Gibbs proved thermodynamically that there is a general relation between the surface adsorption, the lowering of the surface tension and the concentration of the solution. The equation that he deduced can readily be put in the form

$$\frac{dF}{d(\ln p)} = \sigma kT \qquad (1)$$

where p is the partial pressure of the vapor of the adsorbed substance in equilibrium with the surface of the liquid, or it may be the partial osmotic pressure of a substance dissolved in the liquid, σ is the number of molecules adsorbed on the surface per unit area, T is the absolute temperature, and k is the Boltzmann constant 1.37×10^{-16} erg deg^{-1}, and F, which may be called the spreading force, is given by

$$F = \gamma_o - \gamma \qquad (2)$$

where γ_o is the surface tension of the pure solvent (in dynes cm^{-1}) and γ is the surface tension of the solution.

The form of Gibbs' equation represented by Eq. (1) is thermodynamically valid if the film is in equilibrium with the two volume phases and if the law of ideal gases

* This lecture is designed to summarize the author's contributions and present views in this field, but does not adequately describe the work of others.

$$p = nkT \tag{3}$$

is applicable in the volume phases.

Prior to 1910 many different theories of adsorption had been proposed, but none of them had been very successful. In most of these theories the increased concentration of the adsorbed substance near the surface was thought to be analogous to the retention of the earth's atmosphere by the gravitational attraction of the earth. An adsorbed gas was thus regarded as a kind of miniature atmosphere extending out a short distance from a solid substance. In general such theories were called upon to account only for qualitative aspects of the adsorption of gases on solids. Most of the knowledge of adsorption was empirical. Even Gibbs' law had not been verified experimentally.

When I first began to work in 1909 in an industrial research laboratory[1,2], I found that the high-vacuum technique which had been developed in incandescent lamp factories, especially after the introduction of the tungsten filament lamp, was far more advanced than that which had been used in university laboratories. This new technique seemed to open up wonderful opportunities for the study of chemical reactions on surfaces and of the physical properties of surfaces under well-defined conditions. I resolved to try the effect of introducing very small quantities of various gases into a highly evacuated bulb containing a tungsten filament. Since by a McLeod gauge, pressures as low as 10^{-8} atmospheres could be measured, it was possible to observe the disappearance of an amount of gas of less than 0.1 cubic millimeter measured at atmospheric pressure. The use of a tungsten filament presented particular advantages, for this could be heated in high vacuum to temperatures of over 3,000°K, so that all impurities could readily be distilled out of the filament. The ease and accuracy with which any desired temperature could be produced and measured was also important.

When a hot body, such as a filament, is in contact with a gas at atmospheric pressure in a glass bulb, the convection currents and the uncertain temperature distribution in the gas, are factors which greatly complicate any interpretation of observed phenomena involving the interaction of the filament with the gas.

If the gas, however, is at a pressure as low as 100 baryes*, the mean free path of the molecules is many times greater than the diameter of the ordinary tungsten filament. Each molecule which strikes the filament has thus

* A barye or c.g.s. unit of pressure, 1 dyne cm^{-2}, is almost exactly 10^{-6} atmospheres.

made so many collisions with the bulb since its last collision with the filament, that the effective temperature of the gas in contact with the filament may be taken to be the same as that of the bulb. The disturbing effects of convection currents are then entirely eliminated and the rate of arrival of gas molecules at the surface of the filament can be calculated according to the laws of the kinetic theory of gases. This theory leads to the equation

$$\mu = \frac{p}{(2\pi mkT)^{\frac{1}{2}}} \tag{4}$$

where μ is the rate of arrival of the gas molecules expressed in molecules cm^{-2} sec^{-1}, and m is the mass of the molecule. By inserting numerical values this equation becomes

$$\mu = 2.65 \times 10^{19}\, p\, (MT)^{-\frac{1}{2}} \tag{5}$$

where M is the molecular weight of the gas (oxygen = 16) and p is expressed in baryes. By using filaments of small size and bulbs of large size, it was possible to measure experimentally such high rates of disappearance of gas (clean-up) that every molecule that struck the filament disappeared. Under usual conditions, however, the rates of clean-up were far less than this theoretical maximum. The fraction (ε) of all the impinging molecules which reacted on striking the filament could thus be determined.

Working in this way, a systematic study was undertaken of the effects of such gases as oxygen, hydrogen, nitrogen, carbon monoxide, and their mixtures, etc., on filaments of tungsten, carbon, molybdenum, and platinum. I shall refer only to those cases where the experiments have thrown light upon the phenomenon of adsorption.

Clean-up of hydrogen[3]

When a tungsten filament is heated to temperatures of 1,500°K in hydrogen at about 20 baryes pressure, the hydrogen slowly disappears, the pressure decreasing with time as indicated in Curve I of Fig. 1. The pressure falls to a very low value in 10 to 20 minutes. If more hydrogen is introduced, the rate of clean-up is somewhat slower, the pressure decreasing according to Curve II. Although analysis shows the residual gas to be pure hydrogen, the clean-up gradually comes to a standstill.

With a bulb containing two filaments, it is found that the lighting of the second filament does not cause a recovery in the rate of clean-up. This proves that the gas which disappears is not taken up by the filament itself. By keeping the bulb in liquid air, a greater total amount of clean-up is obtained. Such investigations show that the hydrogen which disappears becomes adsorbed on the surface of the bulb, but that the bulb is capable of adsorbing only a limited amount of hydrogen. This hydrogen adsorbed on the glass is capable of reacting with oxygen at room temperature after the filament has been allowed to cool. The adsorbed hydrogen is therefore in a chemically very active state. It was finally proved that the heated tungsten filament dissociates[4,5,6,7,8] a small fraction of the incident hydrogen molecules into atoms, and that these atoms, because of their unsaturated chemical nature, exhibit a strong tendency to be adsorbed on glass. These hydrogen atoms, however, are capable of reacting with one another and forming molecules. From this point of view, it should be impossible to hold on the glass more hydrogen than could form a layer one atom deep.

By cooling the bulb in liquid air the adsorption increased. The maximum amount of hydrogen adsorbed on the glass in these experiments was 0.03 mm^3 per cm^2, measured as molecular hydrogen at atmospheric pressure. This corresponds to $\sigma = 1.5 \times 10^{15}$ atoms of hydrogen per cm^2, which is equal to the number of spheres of diameter 2.8 Å which can be packed per cm^2 into a close-packed hexagonal lattice. The spacing of the adsorbed atoms is probably determined by the arrangement of the atoms in the underlying glass which provide « elementary spaces » in which atoms can be held. If the average diameter of the atoms of the glass can be assumed to be 2.8 Å, the observed maximum amount of adsorbed hydrogen thus agrees well with that to be expected in a monatomic film. If a glass surface saturated with atomic hydrogen at liquid-air temperature is allowed to warm up to room temperature, part of the hydrogen escapes as molecular hydrogen; the rest can be driven off at 300° C. Since adsorbed hydrogen atoms probably react on contact to form molecular hydrogen, then experiments indicate that the surface mobility of the adatoms* is very small at room temperature.

It was shown that the atomic hydrogen can diffuse long distances through glass tubing at room temperature (but not at liquid-air temperature) and can then reduce metallic oxides[9], such as WO_3, CuO, Fe_2O_3, ZnO, or PtO_2,

* J. A. Becker, in *Trans. Am. Electrochem. Soc.*, 55 (1929) 153, has suggested this term for adsorbed atoms.

and can dissolve in platinum sufficiently to raise its resistance[10]. It reacts at room temperature with phosphorus[3] to form PH_3.

Oxygen films on tungsten

When a tungsten filament is heated to 1,500° K or more in oxygen at very low pressures, such as 100 baryes or less, the oxygen reacts[11] with the tungsten to form the oxide WO_3 which evaporates from the filament at these temperatures as fast as it is produced, leaving the surface of the filament apparently clean. At temperatures below about 2,200°K the presence of extremely small amounts of oxygen (10^{-6} mm) decreases the electron emission from a tungsten filament to values that range from 10^{-2} to 10^{-5} of that from pure tungsten, depending on the temperature at which the emission is measured. This modification of the properties of the surface must depend upon the presence of a film which contains oxygen. When the filament temperature is high, such as 2,000° or more, the emission returns to a normal tungsten emission as soon as the oxygen is completely consumed or is removed by vaporizing into the bulb a « getter » such as magnesium. If, however, the filament temperature is as low as 1,500°, complete removal of oxygen from the gas phase, even by introducing caesium vapor as a getter, does not remove the oxygen film on the tungsten surface after it has once been formed. This means that the oxygen from such a film does not evaporate appreciably at 1,500°K. Measurements at higher temperatures show that about half of the adsorbed oxygen evaporates in 27 minutes' time at 1,860° and in about 20 seconds at 2,070°[12]. From the temperature coefficient at this rate of evaporation it can be concluded that it will take about three years at 1,500° to remove half the film by evaporation and that the heat of evaporation is of the order of 160 kcal per gram atom.

This heat of evaporation is far greater than the heat of dissociation of oxygen into atoms; so we have very direct evidence that the forces that hold oxygen to a tungsten surface are comparable to the most powerful chemical forces known. This gives reason for believing that the oxygen film which so greatly decreases the electron emission from tungsten consists of a single layer of oxygen atoms which are chemically combined with the underlying tungsten atoms.

The electron emission from the tungsten filament in the presence of oxygen at temperatures below 1,800° is found to be independent of the pressure

of oxygen, provided that more than about 10^{-3} barye is present. This must mean that the surface is practically completely covered with oxygen and that an increase in oxygen pressure does not cause the thickness of the layer to increase beyond that of a single layer of atoms.

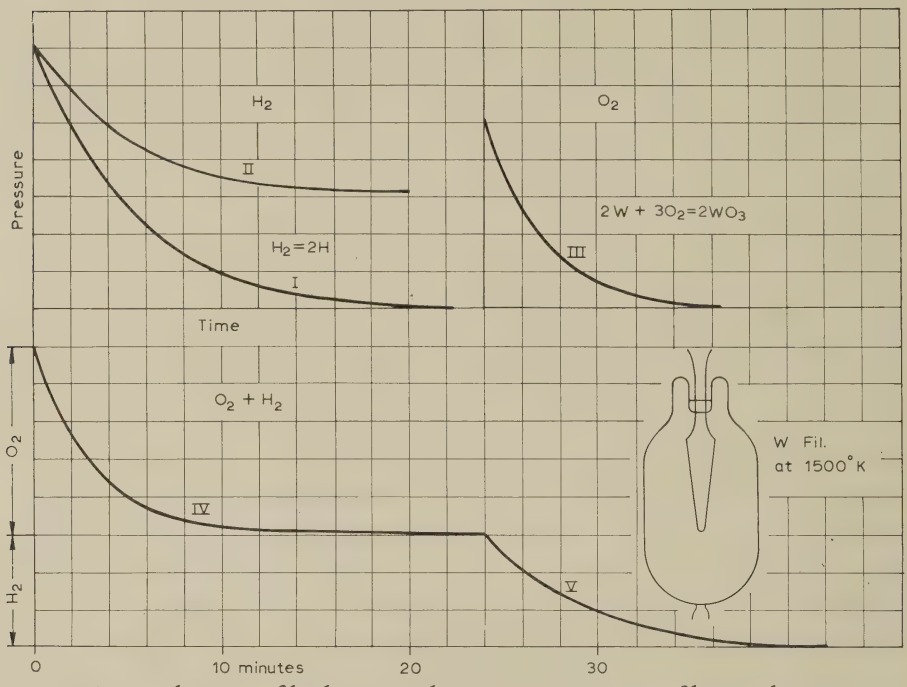


Fig. 1. Clean-up of hydrogen and oxygen in a tungsten filament lamp.

Curve III in Fig. 1 indicates the way in which the pressure of oxygen in the bulb decreases with time when the tungsten filament is maintained at 1,500°K. The rate of disappearance of the oxygen is proportional to the oxygen pressure and there is no fatigue effect, such as was observed during the clean-up of hydrogen.

Interaction of oxygen with hydrogen in contact with tungsten filament

Mixtures of oxygen and hydrogen at low pressures in a bulb containing a tungsten filament behave in an extraordinary manner[13–15]. Typical results obtained with a filament temperature of 1,500° are shown in Curves IV and V of Fig. 1. These curves were obtained with a mixture of 3 parts of hydrogen and 5 parts of oxygen. When the filament was lighted, the gas dis-

appeared at exactly the same rate as shown in Curve III when 5 parts of oxygen alone were present. After about 14 minutes practically all of the oxygen had disappeared. This was confirmed by analysis of the residual gas which was found to be pure hydrogen. This hydrogen, however, did not dissociate in the usual way into atoms and disappear by adsorption on the glass walls as shown in Curve I, but the pressure remained practically constant until after about 24 minutes, when the pressure suddenly began to decrease as indicated by Curve V. This Curve V, however, is identical with Curve I, which is characteristic of the clean-up of hydrogen in absence of oxygen. Repeated experiments with different amounts of oxygen and hydrogen prove that hydrogen does not interfere with the clean-up of oxygen, but that a minute trace of oxygen of about 10^{-3} barye completely prevents the dissociation of hydrogen into atoms by a tungsten filament at 1,500°K. The oxygen thus acts as a catalytic poison. Experiments of this kind can be used to make quite accurate chemical analyses of mixtures of oxygen and hydrogen.

The fact that a monatomic film of oxygen on tungsten does not react with hydrogen at 1,500° is a striking indication that the oxygen is in a condition far different from that of gaseous oxygen. The results, however, confirm our conclusion that the film consists of oxygen atoms which are chemically saturated by the tungsten atoms with which they are in contact.

In view of the fact that an oxygen film on tungsten at 1,500°K does not evaporate in less than a year, it is remarkable that in the presence of hydrogen the beginning of the hydrogen clean-up (Curve V) is so sharp. Since Curve V is exactly like the lower part of Curve I, it appears that once the hydrogen begins to dissociate, the oxygen is suddenly completely removed from the surface; in other words, hydrogen can remove monatomic oxygen films from the tungsten surface if the amount of oxygen on the surface is less than a definite amount. This probably means that the adsorbed oxygen molecules cannot react with hydrogen atoms directly but can react with hydrogen atoms adsorbed in adjacent spaces on the tungsten surface.

Thorium on tungsten[16]

When a tungsten filament which is made from tungstic oxide containing about 1 per cent of ThO_2 is heated to temperatures of 2,800° or more, a minute fraction of the thoria is reduced to metallic thorium. The thoria

exists in the filament in the form of minute spherical particles distributed throughout the tungsten crystals and not at the boundaries of crystals. If the filament is then heated for a period of a few minutes at 1,900 to 2,000°K, the metallic thorium which has been produced at the higher temperatures diffuses slowly through the crystal grains to the crystal boundaries, then diffuses rapidly along these boundaries to the surface of the filament and then spreads over the surface of the filament by surface migration and forms a monatomic film of adsorbed thorium atoms on the surface of the filament. At 2,000° the rate of evaporation of thorium from the filament is so small that sufficient thorium soon accumulates on the filament to form a nearly complete monatomic film. If the temperature is raised to 2,200 or 2,400°, the rate of evaporation of the thorium from the surface increases so much more rapidly than the rate of arrival from the interior by diffusion, that the actual surface concentration decreases greatly.

These changes in the thorium content of the adsorbed film can be studied by measurements of the electron emission from the filament at a standard low temperature, called the testing temperature, which is chosen so low that neither diffusion to the surface, nor evaporation from the surface, causes appreciable changes in the adsorbed film. A convenient testing temperature is 1,500°. At this temperature the presence of adsorbed thorium on the surface may increase the electron emission as much as 10^5-fold over that from a pure tungsten surface.

Such experiments make it possible to investigate the electrical properties of surface films having known amounts of thorium. On the assumption that each thorium atom on the surface acts as a dipole having a definite dipole moment, it is possible to show that the logarithm of the electron emission should increase linearly with the number of thorium atoms on the surface. The experiments showed that for low concentrations of thorium this relation holds approximately.

There are several indications that the adsorbed film of thorium that is formed by diffusion from the interior never exceeds one atom in thickness.

The interaction of carbon dioxide with carbon filaments

If a carbon filament is heated to a temperature above 1,700°K in the presence of carbon dioxide at low pressure, one molecule of carbon monoxide is liberated from every molecule of carbon dioxide[2]. If this carbon monoxide

is pumped out from the bulb and the filament is then heated to 2,300°K, a volume of carbon monoxide is slowly liberated equal to that originally formed from the dioxide. This proves that each carbon dioxide molecule which comes in contact with the filament and reacts, loses one oxygen atom to the filament and thus produces a carbon monoxide molecule. The oxygen atoms thus transferred to the filament form a monatomic film of oxygen atoms covering the surface, these atoms being chemically combined with the carbon atoms with which they are in contact, presumably by double bonds. This adsorbed film on the filament is very stable at 1,700°, but when heated to 2,300°, the film is destroyed, not by the evaporation of the oxygen atoms, but by the breaking of the bonds between the carbon atoms which are attached to the oxygen and the underlying carbon atoms with which they are in contact. Thus the oxygen escapes as carbon monoxide.

From this point of view we see that we can look upon the adsorbed film on the carbon filament either as consisting of adsorbed oxygen, or as an adsorbed film of oriented carbon monoxide molecules, or as carbonyl radicals which are chemically attached by their carbon atoms to the underlying carbon atoms in the filament. It is to be expected that the properties of the adsorbed film would be very different if it consisted of carbon monoxide molecules attached to the underlying surface through their oxygen atoms. These experiments thus led to the concept that the properties of adsorbed films should in general depend on the orientation of the molecules or radicals in the film. It seemed to the writer (in 1915) that evidence of such orientation could be found among the data on the surface tensions of pure liquids.

Surface energies of pure liquids[17,18]

If a prism of liquid having a cross section of 1 sq. cm is divided into two parts by an imaginary plane perpendicular to the axis of the prism, and the two portions of the liquids are then separated, there has been an increase in the surface of the liquid of 2 sq. cm. The total energy theoretically required per sq. cm of new surface to bring about this separation may be called the total surface energy γ_o. This is related to the free surface energy γ, which is equivalent to the surface tension of the liquid, by the relation

$$\gamma_o = \gamma - T\frac{d\gamma}{dT}$$

By measurements of the surface tension, the surface energy γ_o can thus be measured. This quantity represents the potential energy of the molecules which form the surface of the liquid (per sq. cm) in excess of that which the same molecules possess when they are in the interior of the liquid.

In Table 1, data are given for a few substances which serve to illustrate the interrelation[19,20] between the orientations of molecules and other properties of liquids. The latent heat of evaporation (λ) which, according to Trouton's rule, is approximately proportional to the absolute boiling point (T_B) serves as a measure of the energy needed to bring a molecule from the interior of the liquid out into the vapor phase. We have seen that the surface energy γ_o is the energy per unit area needed to form a surface.

The molecular volume V given in this table is the volume of the liquid divided by the number of molecules. The molecular surface S is the surface of a sphere which has the volume V. The extremely low values of λ, the heat of evaporation, per molecule, for helium and hydrogen, indicate that the forces exerted by these molecules on their neighbours are unusually weak. This is in accord with the great stability of the electron pair which forms the K shell of atoms and the covalence bond. The diameters of the helium atom and hydrogen molecule given by the kinetic theory from viscosity measurements, viz. 1.9. and 2.4 Å, correspond to volumes V of only 3.6 and 7.2 Å^3, which are very small compared to the volumes occupied in the liquid. This very open structure of the liquid is again an indication of the weak attractive forces between these molecules.

The effect of replacing one of the hydrogen atoms in the hydrogen molecule by the hydroxyl radical, thus producing water, is to decrease the value

Table 1. Surface properties of molecules

Substance	*Volume V* (Å^3)	*Surface S* (Å^2)	*Boiling point* T_B (°K)	*Heat of evaporation* λ (*erg* $\times$ 10^{-14})	λ/S (*erg cm*$^{-2}$)	γ_o (*erg cm*$^{-2}$)
He	52	68	4.3	0.24	0.35	0.59
H–H	47	63	20.5	1.67	2.7	5.4
H–OH	30	48	373	67	140	118
Ar	47	63	88	11.3	18	35.3
CH_4	64	78	112	16.3	21	—
n-C_8H_{18}	266	200	398	56	28	50.7
n-$C_8H_{17}OH$	260	198	467	82	41.5	50.7

of V from 47 to 30, an indication of strong forces acting between the hydroxyl groups which compress the liquid. A better measure of these forces is given by the 40-fold increase in the value of λ from 1.67 to 67. The surface energy γ_o has been increased 24-fold.

The data for argon illustrate the properties of an atom having a complete electron shell or octet. The fact that in spite of the much larger electron configuration (with a kinetic theory diameter of 2.9) the volume per molecule in the liquid is the same as for hydrogen, shows that the field of force around the molecule is far greater than for hydrogen and helium. The heat of evaporation per unit area λ/S is a very convenient measure of the intensity of this field. With H_2, He and Ar it is about one-half of the surface energy γ_o. The data for methane indicate that this molecule has a value of λ/S, about the same as that for argon. This molecule has a completed octet which shares pairs of electrons with hydrogen atoms. Evidently the presence of the hydrogen atoms does not appreciably alter the field of force; the main effect is to raise the molecular volume, thus raising λ and the boiling point T_B almost in proportion to S.

The values for λ/S for the saturated aliphatic hydrocarbons beyond propane are practically constant and equal to 28. The same constancy is shown in the surface energy γ_o. The data for octane shown in the table are typical. The surfaces of the molecules of the higher-saturated hydrocarbons are thus very much like those of argon atoms, the effect of the chain formation manifesting itself principally in the increase in λ/S from 18 to 28.

The constancy of λ/S is also an indication that the molecules of the vapors of the higher hydrocarbons are approximately spherical in form. The known flexibility of the chain and the surface energy reduction resulting from the more compact form afford ample explanation of this spherical form.

The effect of substituting a hydrogen atom in octane by a hydroxyl radical is illustrated in the last line of the table by the data for *n*-octyl alcohol. There is a small decrease in V paralleling that observed in H_2O, except that now, since each OH group in the liquid cannot be close to many other OH groups, the decrease in volume is considerably less. The large field of force around the OH group is best illustrated by the increase of 26 units in the value of λ. The fact that this increase is less than half of that observed in the change from H_2 to H_2O shows that the OH group in the molecule of the vapor of octyl alcohol is able to bury itself, at least in part, in the approximately spherical molecule.

In spite of the large increase in λ and λ/S in octyl alcohol, the surface en-

ergy γ_o is the same as for octane. This can be explained by the *orientation of the molecules* in the surface layer of octyl alcohol. The great attractive forces exerted by the hydroxyl groups cause them to be drawn down into the interior of the liquid. Thermal agitation tends to counteract this tendency. According to the Boltzmann equation the relative distribution of molecules between two regions of differing energy is measured by $\exp(W/kT)$, where W is the difference in the energy of the molecule in the two states. Now, judging from a comparison of the values of λ for octane and octyl alcohol, the energy necessary to bring an OH group from a hydrocarbon environment out into free space is at least 26×10^{-4} erg. The energy corresponding to kT at room temperature is about 4×10^{-14} erg. Since W is thus more than 6.5 times as great as this, we may conclude that nearly all of the molecules [all but about $\exp(-6.5) = 10^{-3}$] in the surface of octane will be oriented in such a way that the hydroxyl groups do not reach the surface.

We may now understand why the surface energy of octyl alcohol is the same as that of octane. We have previously seen that γ_o can be determined by the energy needed to separate a prism into two parts. We may conceive of this separation as taking place in two steps. The molecules on the opposite sides of an imaginary dividing plane may first be oriented so that the hydroxyl groups are turned away from this plane, leaving only the hydrocarbon parts of the molecule in contact with the plane surface. The two bodies of liquids are then separated from each other along this plane, which would require only the same energy as for pure octane. Because of the orientation of the molecules, γ_o thus differs from that of octane only by the amount of energy needed to turn the molecules around in the interior of the liquid, which is probably negligible.

Referring again to Table 1 we see that a comparison of λ/S with γ_o affords a measure of the effect of orientation. In general, for molecules with uniform fields of force, λ/S is from 0.5 to 0.55 of the value of γ_o.

When, however, a part of the molecular surface has a much weaker field of force than that of other parts, the surface of the liquid consists principally or wholly of the least active parts, so that γ_o is lower than normal. Thus for octyl alcohol λ/S is 0.82 of γ_o while for water it is 1.18, indicating that the water molecule is very unsymmetrical and is strongly oriented at the surface.

At present these illustrations will suffice. In a paper published in 1916 I showed that this theory was applicable to the surface tension of organic liquids in general, including cases of substituted benzene derivatives where the values of γ_o depend to a marked degree on the relative positions of the

substituted groups. Somewhat later W. D. Harkins and his co-workers investigated large numbers of organic substances in this way and completely demonstrated the importance of orientation of molecules in the surface layer of liquids consisting of unsymmetrical molecules.

Oil films on water[18,21]

When a pure saturated liquid hydrocarbon is placed upon the water, it remains on the surface as a drop or lens which has no effect on the surface tension of the surrounding water. If, however, an insoluble fatty or oily substance, such as the common vegetable and animal oils, is placed upon clean water, it spreads out almost instantly as a thin film over the surface. If the motions of the surface are made visible by dusting the surface with powdered talc, it may be seen that, with a limited amount of oil, the film only spreads out sufficiently to cover a definite area, or at least if the area exceeds a rather definite value, the oil has no effect on the surface tension of the water. A comparison of various insoluble organic substances has proved that the spreading tendency depends upon the presence of certain active groups or radicals in the organic molecule, these being the groups which tend to increase the solubility of organic substances in water. For example, pentane, C_5H_{12}, is practically insoluble in water but amyl alcohol, $C_5H_{11}OH$ is relatively soluble. Thus the OH groups in organic molecules exert strong attractive forces on the OH groups in the water molecules and these manifest themselves by an increase in solubility. Similarly the carboxyl group COOH tends to make the lower fatty acids much more soluble in water than the corresponding hydrocarbons.

Hydrocarbons with high molecular weight such as $C_{18}H_{38}$ are extremely insoluble in water. If the carboxyl group replaces the CH_3 group at the end of the chain $C_{18}H_{38}$, one end of the molecule only tends to dissolve in water, whereas the rest of the molecule still retains the insolubility of the hydrocarbons. By spreading over the surface of the water, molecules of this kind can bring their carboxyl group in contact with the water without separating from one another.

An oil film formed in this way must consist of a single layer of molecules packed closely on the surface layer of the water. If there is a surplus of the fatty acid, as compared with the limited area over which it can spread, the endeavor of the carboxyl groups to come in contact with water causes the

molecules to become so crowded at the surface that they stand nearly erect, side by side on the surface. The area occupied by each molecule is thus determined by the cross section of the hydrocarbon chain or by that of the head in contact with water, if this happens to be larger than the cross section of the chain. The thickness of the film is then determined by the length of the hydrocarbon chain.

By dissolving known weights of liquid or solid, oily or fatty substances in a volatile solvent such as hexane, and placing known amounts of these dilute solutions on the water surface, a definite number of molecules can be transferred to the water surface. The oil film can be confined to a given portion of the surface of water in a long tray by a floating strip of paper reaching across the tray. By measuring the forces exerted on the strip of paper, it is possible to measure directly the spreading force F in dynes per cm exerted by an oil film having a given number of molecules of oil per square cm of surface. This surface concentration we shall denote by the symbol σ. Such measurements as these, by which F can be expressed as a function of σ and T, give us then the two-dimensional equation of state of the oil film which corresponds exactly to the three-dimensional equation of state which characterizes ordinary gases and liquids. In fact, the movable paper strip in these experiments is the equivalent of a piston which compresses the gas in a cylinder.

The oil films observed on water may exist as two-dimensional solids, liquids or gases. The film on water obtained from stearic acid $C_{17}H_{35}COOH$ is solid. If it is compressed by a force of 10 dynes per cm exerted against the paper strip, this solidity is manifested if particles of talc are dusted on to the surface and the effects of air currents directed against the surface are watched. The talc particles do not move freely over the surface; if a strong wind displaces them, they return to their original positions when the wind stops, proving a surface rigidity and elasticity characteristic of solids. Other substances such as cetyl alcohol or oleic acid give films which are liquid, since talc particles circulate freely when small forces are exerted by the wind.

By slightly increasing the area available for these films of saturated fatty acids, it is found that the spreading force decreases very nearly to zero, which proves that these films do not act as two-dimensional gases but rather as two-dimensional liquids which have an unmeasurably small two-dimensional vapor pressure. With myristic acid[22], however, a definite two-dimensional vapor pressure of about 0.2 dyne cm^{-2} is observed. Still lower fatty acids give typical gaseous films, but they cannot be studied by this method because

the films are so easily soluble in water that the force exerted by a moving barrier causes them to go into solution.

Adsorbed films on solutions[18,21]

The foregoing method for studying the properties of oil films on water is inapplicable if the film is soluble or is volatile. In such cases measurements must be made in the presence of saturated vapor or saturated solution. Gibbs' equation, Eq. (1), gives us a means of determining the relation between the amount adsorbed on the solution and the spreading force F, in terms of the partial pressure p of the vapor of the adsorbed substance over the liquid or the partial osmotic pressure p of the dissolved substance in the underlying solution. Experimentally F can be measured as the decrease in the surface tension of the pure liquid produced by the presence of the dissolved substance. By the integration of this equation, using the experimentally determined values of F, one can obtain the equation of state of the two-dimensional film whether this is gaseous or liquid or solid.

For very high or very low surface concentrations, Gibbs' equation takes simple limiting forms. At very low concentrations the molecules in the adsorbed films are so far apart that they exert no appreciable forces on one another. Under such conditions σ, the surface concentration, will be proportional to the volume concentration which in turn is proportional to p. If we solve Eq. (1) on the assumption that σ is proportional to p, we find that it leads to the following equation of state

$$F = \sigma kT \tag{6}$$

which is the two-dimensional analogue of Eq. (3), the equation of state of an ideal gas, and it may therefore be called an equation of state of an ideal two-dimensional gas.

The effect of forces acting between the adsorbed molecules is to modify this equation. A two-dimensional analogue of Van der Waals' equation can be written in the form

$$F = \frac{\sigma kT}{(1-\sigma/\sigma_1)} + a\sigma^2 \tag{7}$$

where a and σ_1 are constants.

When the gas phase or the liquid phase contains a relatively high concentration, the concentration of the molecules in the adsorbed film tends to increase to a limiting value σ_1 corresponding to a complete monomolecular adsorbed film such as those that we observed in the study of oil films on water. Although such films show surface elasticity, that is, they are compressible, the forces required to compress the liquid and solid films are so much greater than those required to compress the gaseous film, that the surface compressibility can be neglected as the first approximation, so that we can consider σ_1 to be approximately constant, that is, independent of p and F. Making this substitution in Eq. (1) and integrating, we obtain the following equation which should be applicable for concentrated surface films

$$F = \sigma_1 kT \ln (p/p_o) \tag{8}$$

These two limiting equations are completely in accord with the general relationships found by J. Traube[23]. In Eq. (8) p_o is an integration constant whose value cannot be found from Gibb's equation.

From the Boltzmann equation we can estimate the energy change λ involved in bringing a molecule from the vapor or liquid phase to the surface phase. We thus have

$$\sigma/p = \text{const} \exp (\lambda/kT) \tag{9}$$

Traube found that with molecules of aliphatic compounds having different lengths of hydrocarbon chains, the ratio F/p for dilute solutions (which should be proportional to σ/p) increases about threefold for each CH_2. When this is interpreted in accord with Gibb's and Boltzmann equations, we conclude that the energy λ involved in the adsorption of these molecules increases linearly with the length of the chain. This means that each CH_2 group in the molecule must be similarly situated in the surface film. In other words, in these dilute films where there is much free water surface available, the hydrocarbon molecules must lie flat on the surface. With the concentrated films in which σ is constant so that Eq. (8) applies, there is no available free surface of water and the molecules must stand nearly erect on the surface.

These two cases given by Eqs. (6) and (8) are only limiting cases and the complete equation of state for the whole range from dilute to concentrated films would be more complicated, since it must involve the intermediate

states between those in which the molecules lie flat on the surface and stand erect on the surface. The experimental difficulties of the accurate measurements of the surface tensions of solutions are such, that relatively little work has been done on the equation of state of these adsorbed films on solutions as compared with the large amount of work done by N. K. Adam[22] and others on the equations of state of films of insoluble substances on water.

The molecules in adsorbed films on liquids are of course free to move over the surface of the liquid except in so far as the film itself may possess the properties of a solid.

Adsorbed films on solids

Adsorbed films on solids may exist in three states corresponding to two-dimensional gases, liquids or solids. A new factor now appears, however, which was not present in the case of adsorbed films on liquids. The forces exerted by the underlying solid on adsorbed atoms or molecules tend to hold the molecules in definite positions fixed by the lattice of the solid. The solid surface is thus to be looked upon as a type of checker-board containing definite numbers and arrangements of elementary spaces[13,24], each of which is capable of holding an adsorbed molecule. To move a molecule from one elementary space to another thus presumably requires something analogous to an activation energy; only those molecules possessing a sufficient kinetic energy to pass over a potential barrier can succeed in hopping from one elementary space to another[25]. On this basis we should expect a surface mobility at high temperatures which would disappear at low temperatures. The logarithm of the rate of mobility, or the surface diffusion coefficient, should vary linearly with the reciprocal of the absolute temperature and the slope of this line should be proportional to the activation energy.

In general the surface diffusion coefficient increases with σ, for the ability of adatoms to cross the potential barrier is not determined solely by the thermal agitation of the molecules but depends on $dF/d\sigma$, since differences in the value of F over the surface contribute to the mobility.

We may thus consider that in general the adatoms on solids move over the surface by hopping between elementary spaces. If the adatoms move nearly independently of one another, so that they migrate freely on to all unoccupied portions of the surface, the adsorbed films can be regarded as a two-dimensional gas in spite of the fact that the atoms tend to occupy

definite positions. Such films constitute a two-dimensional crystalline gas, the crystalline character being imparted by the underlying lattice. If attractive forces exist between the adatoms which are sufficiently strong to cause them to form a definite two-dimensional condensed phase in equilibrium with a two-dimensional vapor phase, we clearly have to do also with a two-dimensional solid or liquid. If the mobility is high, this condensed film may have properties characteristic of liquids; with no mobility at lower temperatures, the conditions will be analogous to that of a two-dimensional glass. A two-dimensional solid analogous to ordinary three-dimensional solids would exist only if the forces exerted by the adatoms on each other can keep them from slipping past one another.

Condensation–evaporation theory of adsorption on solids

When molecules of a gas in contact with a solid impinge individually on the solid, they may either condense or may rebound from the solid as though elastically reflected. Those molecules that condense may subsequently evaporate. There is much theoretical and experimental evidence that a true reflection of molecules under these conditions is a rather abnormal occurrence, although the specular reflection of molecular rays from certain crystalline surfaces shows that it sometimes exists. In the great majority of cases, however, the observed phenomena indicate that the larger part of all incident molecules condense on the surface and reach thermal equilibrium with it before they evaporate[26,27]. With such gases as hydrogen and helium, accommodation coefficients materially less than unity have been found. In general these occur with gases striking solids at such temperatures that the rate of evaporation may be assumed to be so high that the life of the condensed molecule is of the order of 10^{-13} seconds, which is about the time required for a molecule to perform a single thermal oscillation on the surface. Under these conditions it is not surprising that thermal equilibrium is not reached.

When the rate at which molecules impinge on the surface is μ, as given by Eq. (4), and ν is the rate at which they evaporate (molecules cm^{-2} sec^{-1}), then the rate at which they accumulate on the surface is given by

$$\frac{d\sigma}{dt} = \alpha\mu - \nu \qquad (10)$$

where α, the condensation coefficient, in the majority of cases is equal to unity, but in any case can never exceed unity. The rate of evaporation ν is in general dependent on the temperature and on σ, the surface concentration. Of course it also depends on the nature of the solid surface on which adsorption occurs. If the surface is strictly homogeneous, ν may be a function of σ and T only for a given surface, but it may be possible that different portions of the surface are capable of exerting different forces on adatoms, so that ν and σ may not be uniform over the surface.

In a stationary state when σ is not changing with time, the general condition that must be fulfilled is

$$\alpha\mu = \nu \tag{11}$$

If we divide the rate of evaporation ν by σ, the number of atoms per square cm, we obtain the average probability per second for the evaporation of the individual atoms. The reciprocal of this (τ) is thus the average life of an adatom on the surface. Thus we have

$$\tau = \sigma/\nu \tag{12}$$

This time lag that exists between the condensation and the evaporation of adatoms may thus be looked upon as the fundamental cause of the adsorption of gases on solid surfaces.

In general, ν should increase rapidly with temperature like the vapor pressure of substances. Thus the logarithm of ν should increase approximately linearly when plotted against the reciprocal of the absolute temperature, and the slope of this line is proportional to the heat of evaporation and is a measure of the magnitude of the forces by which the adatoms are held on the surface. Thus ν should be approximately given by an equation of the type

$$\nu = \text{const. } \exp(-\lambda/kT) \tag{13}$$

where λ is a measure of the energy required to remove an adatom from the surface. The reason for the large variations of ν for different substances is due mainly to variations of λ rather than to differences[28] in the constant factor in Eq. (13). This is indicated by such approximate laws as Trouton's rule.

The forces acting between atoms and molecules are normally of extremely

short range [27,29], so that the forces acting on an adatom, which determine the magnitude of λ, and therefore of ν, depend mainly upon the atoms with which any given adatom is in contact. When the gas pressure is raised or the temperature is lowered so that σ increases to such a point that there is no longer room for any additional molecules in the first layer in contact with the solid, a still further increase in σ would require that a large number of adatoms must be contained in a second layer. Now these adatoms in the second layer cannot be in *contact* with the solid surface on which the primary adsorption occurs, and therefore for these atoms λ_2 should differ from the value of λ_I that applies to the adatoms in the first layer. Since λ occurs in the exponent of Eq. (13), a relatively small change in λ is sufficient to cause a marked difference in the value of ν.

Thus when the adsorbed substance is not nearly identical in its properties with the substance on which adsorption occurs, we should expect the value of ν for atoms in the first and atoms in the second layer to be greatly different from one another. Naturally two cases may arise[28]: ν_2 may be either greater or less than ν_I.

Case 1: $\nu_2 < \nu_I$. If ν_2 is less than ν_I, the atoms in the second layer are held by stronger forces to those in the first layer than these latter are by the atoms of the underlying solid. There is therefore a tendency for the atoms in the first layer to form clusters and on these clusters the second and third, etc., layers begin to form long before the whole of the first layer is covered[27]. Such phenomena are of common occurrence. For example, when mercury, cadmium or iodine is vaporized in vacuum and is condensed on a glass surface, at a not too low temperature, discrete crystals of the condensed substances form on the glass. This is a direct indication that these atoms exert greater forces on one another than they do on the underlying glass.

If the glass surface is maintained at a temperature so high that these nuclei do not form, then the glass surface *appears* to reflect all the incident atoms, for they evaporate from the glass surface far more rapidly than they do from a cadmium surface at the same temperature. Such observations were made by R. W. Wood, who attempted to explain them by a large reflection coefficient. He believed that experiments indicated that molecules of mercury incident at low pressures on cold glass surfaces were completely reflected at temperatures above $-90°$C, but were completely condensed below that temperature.

From our present viewpoint such a critical temperature has nothing to do with a true reflection but is dependent on the fact that with a given stream

of mercury or cadmium atoms there is a definite temperature below which evaporation of the individual adatoms cannot take place fast enough to prevent accumulation sufficient to form a monatomic film, so that all further evaporation at these low temperatures ceases. Experiments show conclusively that at all temperatures the mercury atoms condense, but that, if the temperature conditions are favorable, single atoms re-evaporate from the glass at fairly low temperatures.

It is evident therefore that those cases in which ν_2 is less than ν_1 are characterized by the growth of crystals from nuclei and do not lead to the formation of monomolecular films but rather to discrete crystal particles.

Case 2: $\nu_2 > \nu_1$. In this case, as the pressure is gradually raised or the temperature is lowered, σ increases until a monomolecular film is formed, but it then takes a considerable decrease in temperature or increase in pressure before a second layer begins to form. These conditions therefore commonly lead to the formation of films which do not exceed a molecule in thickness over a wide range of experimental conditions. This case therefore is characterized by typical adsorbed films.

Adsorption isotherms

The fundamental equation governing the amount of adsorbed substances on a solid surface is given by Eq. (11). To put this into a definite form relating the pressure p of the external gas and σ, the surface concentration, we need only to be able to express α and ν as functions of σ and T. The functional relation of ν to σ depends not only on the forces exerted by the underlying solid, but on the forces acting between adatoms. Furthermore we must consider that the incident molecules corresponding to μ cannot all go directly into elementary spaces on the bare surface, but many of them will make their first contact at places already occupied by adatoms. An important aspect of the problem of the adsorption isotherm is the determination of the manner in which these incident atoms find places in the first layer. Many atoms may temporarily be forced to occupy places in the second layer from which they can either evaporate at a much higher rate than from the first layer, or may migrate until they drop into positions in the first layer.

It is natural under these conditions to make assumptions which are as simple as possible and to see whether the resulting equations can find a field of application[24]. If the adatoms do not exert appreciable forces on one an-

other, we may thus assume that the life of τ of each one is independent of the presence of other atoms on the surface. Thus by Eq. (12), ν is proportional to σ.

Instead of dealing with the surface concentration of σ it is often convenient to use the covering fraction Θ defined by

$$\Theta = \sigma/\sigma_1 \tag{14}$$

where σ_1 is the surface concentration in a complete monomolecular film.

Thus we may put

$$\nu = \nu_1\Theta \tag{15}$$

where ν_1 represents the rate of evaporation from a completely covered surface.

When molecules incident on the surface strike a part which is unoccupied by other adatoms, we may assume that the fraction α_0 condenses. The fraction of such surface which is bare may be represented by $1-\Theta$. Therefore the number of incident atoms which go directly into the first layer may be put equal to $\alpha_0 (1-\Theta) \mu$. The fate of the other incident atoms, viz. those that first strike adsorbed atoms, will depend on many factors, some of which we shall discuss later. A very simple, although not very probable, assumption is that all these atoms re-evaporate so fast that they do not have opportunities to find positions in the first layer. On these assumptions we find

$$\alpha\mu = \alpha_0 (1 - \Theta) \mu \tag{16}$$

Substituting this and Eq. (15) into Eq. (11) and solving for Θ, we obtain the following simple adsorption isotherm,

$$\Theta = \frac{\alpha_0\mu}{\nu_1 + \alpha_0\mu} \tag{17}$$

This equation has been found to apply with reasonable accuracy to a surprisingly large number of cases of adsorption on plane surfaces. Considering the nature of the simplifying assumptions made in its derivation, it should of course not be looked upon as a general equation for the adsorption isotherm. The cases where this equation is most likely to apply are those in which the

adsorption occurs only in elementary spaces which are so far separated from one another that the adatoms in the separate spaces do not exert appreciable forces on one another. This can justify the assumption of Eq. (15). Also in this case the condensation may reasonably occur according to Eq. (16), because if a given space is occupied, which has a probability proportional to Θ, the incident atom cannot merely slip into an adjacent elementary space but must fall on to an area on which it is held with so little force that it evaporates before it can move into any vacant elementary space. These assumptions will give us an equation like Eq. (17) except that the significance of Θ and of the coefficient α_o is somewhat modified.

Recent experiments have shown that in the mechanism of condensation mobility plays an important part[30]. Thus in general an incident molecule striking a surface already covered may be assumed to move an appreciable distance before finally settling into a position in the first layer. Certainly if the surface is homogeneous so that all parts of it are available for adsorption, an incident molecule striking an isolated adsorbed molecule can hardly be regarded as being even temporarily in a second layer. Such an atom will slip into a position in the first layer before having any occasion to rebound or evaporate from the surface. An atom cannot be in a second layer even temporarily unless it is supported by at least three, or more often four, atoms in the underlying layer. Even if there is no mobility, the probability that an incident atom could occupy a place in the second layer would be proportional to Θ^n, where n is at least as great as 3 or 4. If the rate of evaporation is very high, we might expect these atoms to evaporate before finding places in the first layer. On this basis, therefore, instead of Eq. (16), the expression for the rate of arrival of atoms in the first layer should be

$$\alpha\mu = \alpha_o (1 - \Theta^n)\, \mu \qquad (18)$$

Some experiments were made to test the reasonableness of these conclusions. The bottom of a tray was covered with steel balls ($\frac{3}{8}$ inch diameter) closely packed into a square lattice and cemented into position. This surface thus possessed many of the features of a homogeneous crystal surface, the steel balls corresponding to the individual atoms. When other balls of the same size were thrown on to the surface, they occupied definite elementary spaces, each being in contact with four underlying balls. The number of such elementary spaces (except for an edge correction) was the same as the number of balls which were cemented into place (zero layer). A large number of

balls, sufficient to cover the fraction Θ of the available spaces, was placed in the tray (in first layer) and the tray was shaken to give a random distribution. A small number of additional balls were then dropped at random from a height of 5 cm to the surface, and the number of these which went into the second layer was counted. It was found that the probability P that a given incident ball would occupy a position in the second layer was quite accurately given by

$$P = \Theta^{4,5} \tag{19}$$

The fraction of the incident balls finding positions in the first layer was thus $1-\Theta^{4,5}$. A comparison of this with Eq. (18) gives a value of $n = 4.5$. The reason that n is greater than 4, the number of underlying atoms, is probably that the kinetic energy of the balls causes some of them to roll from their positions of first contact.

Applying these results to adsorption, we should expect that, until Θ is very close to unity, all atoms incident on the surface should reach positions in the first layer without any opportunity of evaporation or reflection, even if the evaporation rate in the second layer is very high.

Effect of forces acting between adatoms[28]

The fact that two adatoms cannot occupy the same elementary space at the same time must mean that they exert repulsive forces on one another. This will manifest itself in the equation of state of the adsorbed atoms by a factor such as the $1-\Theta$ in the denominator of the first term of the second member of Eq. (7). This means that the spreading force tends to rise indefinitely as Θ approaches the value unity. Combining this equation of state with Gibbs' equation, and assuming $\alpha = 1$, we obtain for an adsorption isotherm the equation

$$\ln (\nu/\Theta) = \ln [1/(1-\Theta)] + 1/(1-\Theta) + \text{const.} \tag{20}$$

Thus we see that the rate of evaporation should increase indefinitely as Θ approaches unity. It is just this effect which limits the amount of material in typical adsorbed films on liquids or solids to that contained in a monomolecular layer.

The forces holding adatoms on the surface in characteristic cases of adsorption are usually far greater than those acting between adatoms. If this were not the case, we would be dealing normally with the case in which ν_2 is less than ν_1, so that we would not have adsorbed films but crystal nuclei. The effect of these strong forces originating from the underlying surface is to polarize the adatoms. If these are all of one kind, they thus tend to become similarly oriented dipoles which repel one another with a force varying inversely as the fourth power of the distance between them. There may also be attractive forces of the Van der Waal's type, but these will vary with a much higher power of the distance. The dipole forces will have a range of action far greater than other forces involved. A knowledge of these factors which are probably important in most cases of adsorption can best be acquired by a detailed study of some one example in which quantitative determinations of all the factors are possible. The example that I have chosen for this purpose is that of adsorption of caesium vapor on tungsten, for in this case we can measure with great precision the surface concentration σ as well as the rates of evaporation ν of atoms, of ions, and of electrons[30]. Thus we are able to express these values of ν_a, ν_p and ν_e as functions of Θ and T. These measurements enable us not only to determine the forces acting between the adatoms but also to determine the electrical properties of the adsorbed films.

Caesium films on tungsten

The ionizing potential of caesium is 3.9 volts, which is lower than that of any other chemical element. The heat of evaporation of electrons from tungsten corresponds to 4.6 volts. Thus the energy necessary to detach an electron from a caesium atom is 0.7 volts less than that necessary to pull an electron out of metallic tungsten. It is therefore not surprising that experiments[31,32] show that every caesium atom which strikes a tungsten filament at high temperature loses its electron and escapes as a caesium ion. The electric current that thus flows from the tungsten is a quantitative measure of the number of atoms of caesium that strike the filament. Since currents of 10^{-17} A can be measured by an electrometer, it thus becomes possible to detect a pressure of caesium vapor so low that only 100 caesium atoms per second strike the surface of a filament.

The escape of the caesium ions from the tungsten surface is an evaporation

phenomenon. If the temperature is below about 1,100°K, the rate of evaporation of the ions may be so low that it does not keep pace with the rate at which the atoms arrive, so that there is an accumulation of adsorbed caesium on the surface. As a matter of fact, the rate of evaporation of the adsorbed caesium from the surface at a thousand degrees is about the same as that from a surface of metallic caesium at room temperature (300°K). Thus from Trouton's rule we should expect the heat of evaporation of caesium adatoms to be about three times as great as the heat of evaporation of caesium itself.

Such large forces between the adsorbed caesium atoms and the underlying tungsten surface are to be expected as a result of the fact that the caesium tends to lose its electron when close to the tungsten surface. Thus the positively charged caesium ion induces into the conducting tungsten surface a negative charge, which exerts a force of attraction on the ion (the «image force») equal to $e^2/4x^2$, where x is the distance of the ion from the surface. This image force is of ample magnitude to account for the strong forces holding caesium on tungsten.

If a thoriated tungsten filament is used, and this is given the special heat treatment required to bring a complete monatomic film of thorium to the surface, the heat of evaporation of electrons falls to about three volts, which is 0.9 of a volt lower than the ionizing potential of caesium. In accord with this fact the experiments show that caesium atoms are not converted into ions by an activated thoriated filament, nor is there any observable tendency for the caesium to become adsorbed on the filament.

If, with a pure tungsten filament in presence of caesium vapor, the temperature is maintained low enough to permit an adsorbed film of caesium to be formed, the positively charged adatoms, which cause a positive contact potential against the pure tungsten surface, have the effect of lowering the heat of evaporation of the electrons. When such an amount of caesium is present on the surface that the heat of evaporation is materially below 3.9 volts, the tendency of the filament to rob incoming caesium atoms of their electrons and thus allow them to escape as ions is lost. This means that ν_p, the rate of evaporation of ions, becomes very small as Θ, the fraction of the surface covered by caesium atoms, increases.

At temperatures of about 700°K, in presence of caesium vapor saturated at room temperature (pressure about 10^{-9} atmosphere), Θ increases to approximately 0.7 and the heat of evaporation has then been lowered to such a point that the electron emission is 10^{22} times greater than that of a clean tungsten filament at the same temperature.

Within the last three years, Dr. J. B. Taylor and I have made a detailed study[28,30] of the rates of evaporation of atoms, ions and electrons from these caesium films on tungsten as functions of Θ and T. In order to measure Θ, a method was devised for determining σ, the number of adsorbed atoms per square cm of tungsten surface. Two methods were found. When Θ is less than 0.08, a sudden heating or flashing of the filament at temperatures above 1,300° causes every caesium adatom to escape from the filament as an ion so that the ballistic kick measured with the galvanometer gives directly the value of σ. The second method, which is applicable at any values of σ (even those corresponding to polyatomic layers), involves the evaporation of the adatoms as atoms, in the presence of a retarding field which prevents the escape of ions. This burst of atoms falls on a parallel neighboring tungsten filament heated above 1,300° from which these atoms escape as ions. The ballistic kick of current from this second filament thus measures σ on the first filament. We call this the two-filament method of measuring σ.

The measurements of σ showed that as the caesium pressure is increased or the filament temperature lowered, σ increases to a definite limiting value of σ_1 which is 4.8×10^{14} atoms per square cm of apparent filament surface. A study of the crystal habits of tungsten has shown that the surface lattice of surfaces etched by evaporation contains 1.425×10^{15} atoms per square cm. Since the diameter of the caesium atoms is almost exactly twice that of tungsten, and because of the tendency of the adatoms under the strong forces exerted by the tungsten, to occupy definite elementary spaces on the surface, we conclude that the maximum number of caesium adatoms is one quarter the number of tungsten atoms and therefore the true value of σ_1 is 3.563×10^{14} atoms per square cm. Comparing this with the observed or apparent value of σ_1 it appears that the true surface of the tungsten filament is 1.347 times the apparent surface, this difference being due to the slight etching of the filament surface by evaporation at high temperatures.

A study of transient states during which Θ increases or decreases with time has proved conclusively that the phenomenon of condensation or evaporation goes on independently of one another, the condensation being dependent on μ, while the evaporation ν is strictly a function of Θ and T only, and does not depend upon the way the surface film has been formed.

The experiments show that within the accuracy of the experiments (about 0.5%) the condensation coefficient α is always equal to unity even when Θ is as great as 0.98. This proves that the incident atoms, which under these conditions must nearly all strike adatoms, can slide around in a second layer

until they find positions in the first layer. The experiments prove, however, that the number of atoms which exist at any time in the second layer is extremely minute, of the order of 10^{-7}. The atoms in the second layer possess very high surface mobility.

The rate of evaporation of atoms ν_a increases at any given temperature extremely rapidly as Θ increases. Thus at 1,000°K an increase of Θ from 0.1 to 0.9 causes a 10^{11}-fold increase in ν_a. This indicates very strong repulsive forces between the adatoms in agreement with the fact that these adatoms tend to be positively charged as indicated by the effect of the film in increasing the electron emission. It has been possible to develop this relationship between ν_a and ν_e into a quantitative theory.

A single caesium adatom on a tungsten surface may be regarded as an ion held to the metal by its image force. The image and the ion thus constitute a dipole, having an electric moment M, oriented with its axis perpendicular to the surface. Because of the strong electric fields close to the ion when it is adsorbed on the surface, we should expect the conduction electrons in the metal to be drawn towards the ion so that the dipole moment should be considerably less than we would calculate for a caesium ion at a distance from an ideal metal surface equal to its radius. The experimental values of M have actually been found to be 16.2×10^{-18}, whereas we calculate 25×10^{-18} for a spherical caesium ion in contact with an ideal conducting plane.

The force f between two such adion dipoles is given by

$$f = (3/2)\, M^2/r^4 \tag{21}$$

where r is the distance between the adions.

We may now work out the equation of state of the adsorbed caesium films in terms of these forces by means of Clausius' virial equation which for surfaces takes the form

$$F = \sigma kT + (1/4)\, \sigma\, \Sigma (rf) \tag{22}$$

where the summation is to extend over all adatoms which act on any one adatom. The forces f are of two kinds: first, the long-range forces which correspond to the dipole repulsion given by Eq. (21), and second, the short-range forces acting between atoms in contact which prevent any two from occupying a single elementary space at the same time. These short-range

forces may be taken into account by dividing the second member of Eq. (6) by $(1-\Theta)$, as has already been done in Eq. (7). In this way by an integration process it has been possible to derive the general equation of state for adsorbed atoms which repel as dipoles. This equation is

$$F = \sigma kT/(1-\Theta) + 3.34\,\sigma^{5/2}M^2 + 1.53 \times 10^{-5}\sigma^2 T^{1/3}M^{4/3}I \qquad (23)$$

where I is an integral whose numerical value can never exceed 0.89 and which can be obtained from tables and curves from the value of M, σ and σ_1.

The spreading force F calculated in this way cannot be measured directly for a solid surface but it can be related to the rate of evaporation ν_a by means of Gibbs' equation

$$\frac{dF}{d \ln \nu_2} = \sigma kT \qquad (24)$$

By substituting in this equation the values of F from Eq. (23), ν_a can be calculated in terms of M. Actually we have reversed the process. From the experimentally determined values of ν_a as functions of σ and T, we have calculated F by Eq. (24) and from these by Eq. (23) have obtained M. These values of M are found to be functions of σ but are not appreciably dependent on T, although a slight dependence is indicated by the form of Eq. (23).

A test of this theory can be made since the values of M obtained from ν_a may be compared with values of M obtained from the contact potential which may in turn be obtained from measurements of ν_e. The contact potential V of a surface covered with an adsorbed film as compared with that of a pure metal surface is given by

$$V = 2\pi\sigma M \qquad (25)$$

Furthermore the electron emission ν_e is related to the contact potential V by the Boltzmann equation

$$\nu_e/\nu_w = \exp\,(Ve/kT) \qquad (26)$$

where ν_w is the electron emission from pure tungsten at the same temperature. The full line curve in Fig. 2 gives values of V calculated by Eq.

(25) from M as determined from ν_a. The points shown by small circles represent values of V obtained from ν_a by Eq. (26).

The values of V obtained by these two independent methods agree nearly perfectly when $\Theta < 0.5$. The deviations at higher values of Θ seem to indicate that for high values of Θ the short-range forces are somewhat greater than those given by the factor $1-\Theta$, the denominator of the first term of the second member of Eq. (23). Calculation shows that for a value of $\Theta = 0.75$, that part of the spreading force which is due to the short-range forces is actually 45 percent greater than is given by the first term in the second member of Eq. (23).

It is also possible to calculate the contact potential from data on ν_p, the rate of evaporation of ions from the surface. The values of ν_a, ν_e and ν_p must be so related to one another that they give concentrations of atoms, electrons and ions in the vapor space near the filament which agree with the thermodynamical requirement for equilibrium among these particles. We may thus put

$$n_e n_p / n_a = K \tag{27}$$

where K is the equilibrium constant that can be determined from the ionizing potential in accordance with the Saha equation. When this is done, and we combine with the Boltzmann equation and the Dushman equation for the electron emission from tungsten, we obtain

$$\ln (2\nu_p) = \ln \nu_a + (e/kT)(V_w - V_i - V) \tag{28}$$

where V_i is the ionizing potential of caesium, and V_w is the heat of evaporation of electrons from tungsten. The values of the contact potential V calculated from ν_p in this way are indicated in Fig. 2 by crosses. These points lie on the curve obtained from ν_a.

This agreement of the values of V obtained by these three methods shows that our theory gives a complete account of the electrical and chemical properties of moderately dilute adsorbed films of caesium on tungsten. It proves also that the surface of these tungsten filaments was essentially homogeneous, so that the probability of evaporation of any adatom or adion was independent of the position of the atoms on the surface and was determined wholly from the value of σ at that point.

The experiments showed, however, that this conclusion, although true for over 99 per cent of the surface, did not hold exactly. Deviations at very

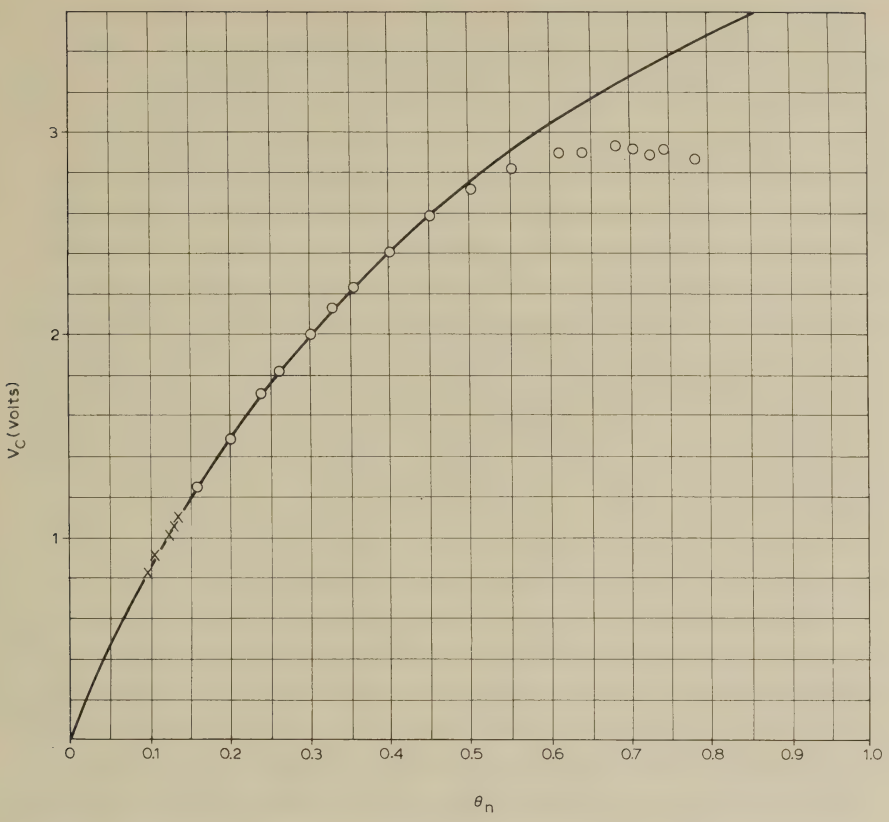


Fig. 2. Contact potentia lof caesium films on tungsten against clean tungsten.

low values of Θ indicated that about 0.5 per cent of the surface consisted of what we may call active spots which adsorbed caesium far more strongly than the rest of the surface, so that the heat of evaporation of these areas was about 37 per cent greater than that for atoms on the normal part of the surface. Experiments also showed that adsorption on this part of the surface was of the type indicated by Eq. (17): the simple type of adsorption isotherm. This means that the atoms adsorbed in the active areas did not exert appreciable forces on one another. Evidently the active spots consist of separated elementary spaces distributed over the surface, probably near grain boundaries or at steps in the crystal faces.

A variation of the dipole moment M with σ results from the depolarizing effect of neighbouring dipoles. The electric fields due to these dipoles can be calculated by an integration process similar to that used in calculation of F, and are of the order of 5×10^7 volts cm^{-1}.

When a tungsten filament is heated to about 1,100° in caesium vapor and there is an accelerating field drawing ions from its surface, two coexistent surface phases may occur. For one of these Θ is about 0.15, while in the other it is very close to zero. The atoms that strike the less concentrated phase evaporate as ions, while those that strike the concentrated phase evaporate as atoms. The phase boundary is perfectly stable and stationary at a definite temperature in the presence of a given pressure of caesium. If the temperature is raised slightly, the phase boundary moves towards the concentrated phase, so that the whole filament gradually becomes bare; a lowering of the temperature causes the whole surface to become covered with the concentrated phase. A detailed analysis of the mechanism at the boundary between the phases which involves diffusion from one phase to the other, makes it possible to measure the surface diffusion coefficient D. Results have shown that

$$\log D = -0.70 - 3060/T$$

From the temperature coefficient of D it can be calculated that the surface diffusion activation energy is about 0.6 volts. This means that between each of the elementary spaces there is a potential barrier of the height of 0.6 volts over which the adatoms must hop in order to migrate over the surface.

The experimental methods involved in these studies of caesium films on tungsten are capable of very great accuracy and sensitiveness, so that they seem to offer a rich field for the detailed study of adsorption phenomena. Dr. Taylor and I are continuing work in this field. We are planning to make accurate comparisons between the properties of films of adsorbed caesium, rubidium and potassium. We have developed a method of introducing definite small amounts of oxygen by diffusion through a heated silver tube. In this way known numbers of oxygen atoms may be placed on the surface of a tungsten filament thus forming negative dipoles. These attract the positive caesium dipoles which tend to form clusters around them, forming a kind of two-dimensional colloidal distribution of caesium. We hope by the detailed study of such systems to learn the effects not only of repulsive but also of attractive forces between adatoms. Experiments are also in progress to study the adsorption of caesium on tungsten surfaces containing known numbers of adsorbed thorium atoms.

In such ways as these, together with the methods involving the spreading of oil films on water, it becomes possible to determine the equations of states

of two-dimensional gases, with nearly the same degree of accuracy as in the case of three-dimensionals, but with the further advantage that the conditions are especially favorable for the determination of the mechanism of all of the processes involved.

Types of adsorption

The classical kinetic theory of gases, as for example in the treatment of viscosity by Sutherland and of the continuity of the transition from gas to liquid by Van der Waals, led to the recognition of attractive forces between molecules at large distances and of strong repulsive forces at short distances. The chemist has long known that exceptionally large attractive and repulsive forces are associated with the chemical union between adjacent atoms, which he represents by the valence bond (primary valence) and that weaker forces, which he has called secondary valence forces, usually correspond to other types of chemical combinations. The physicist has studied the forces between charged particles, such as ions and dipoles, and more recently has discovered the interchange forces, which are best explained in terms of quantum mechanics.

In the structure of matter there can be no fundamental distinction between chemical and physical forces: it has been customary to call a force *chemical*, when it is more familiar to chemists, and to call the same force *physical*, when the physicist discovers an explanation of it. There are also usually no sharp dividing lines between attractive and repulsive forces or between the various kinds of attractive or repulsive forces. Nevertheless a recognition of various types of forces responsible for the stability of matter proves useful in classifying natural phenomena. Thus in a qualitative way we may consider the following types of forces[29].

(1) Coulomb forces between ions or ions and electrons varying with $1/r^2$ where r is the distance between ions. The best examples of these forces are in salt-like substances.

(2) Forces between dipoles which vary with $1/r^4$ and depend on the orientation of the dipole.

(3) Valence forces, associated with the sharing of electrons between atoms.

(4) Van der Waals' attractive forces, which depend on the mutual polarizability of molecules. These forces are usually considered to vary with $1/r^7$.

(5) Repulsive forces due to the mutual impenetrability of completed elec-

tronic shells. It is primarily these which determine the collision areas of molecules in the kinetic theory. Born and Mayer[33] find that the potential energy of these repulsive forces between two completed shells is given by

$$A \exp [(r_1 + r_2 - r)/r_0]$$

where r_1 and r_2 are the effective radii of the two shells and r_0 is a universal constant equal to 0.435 A, while A is another universal constant. This means that this type of repulsive force between two atoms can be expressed as a function of the distances between the *surfaces of the atoms*, this function being the same for nearly all atoms (or molecules) which have completed shells, regardless of their electric charge. From a consideration of several of the other properties of solids and liquids I had previously drawn a similar conclusion[20], that the repulsive forces should be regarded «as surface forces which should be expressed as functions of the distances between the surfaces of the atoms (fixed by the electron orbits), rather than in terms of the distances between the centers of the atoms». A consideration of Van der Waals' forces showed that for these also the «intensities of the fields around different non-polar molecules are practically identical when regarded as surface forces».

The fact that these repulsive forces, according to Born and Mayer, decrease to $1/e^{th}$ value for each increment of 0.435 A° in the distance between the atoms, indicates that they have a very small range of action.

(6) *Electron pressures* – The force that counterbalances the Coulomb attraction of the electrons and ions in the alkali metals – and probably in other metals – is that due to the pressure of the Fermi electron gas.

Since all of these forces can be effective at the surface as well as in the interiors of solids and liquids, they must take part in adsorption phenomena. There should thus be various types of adsorption corresponding to the several types of forces which hold the atoms or molecules on the surface. Let us consider some examples:

Caesium on tungsten – The caesium ions are held by Coulomb attractive forces (here a modified image force) to the underlying metal. The corresponding repulsive forces which hold the ion a definite distance from the surface (and thus determine the dipole moment M) result from the pressure gradient in the Fermi electron gas which extends beyond the lattice of tungsten atoms. The forces between the caesium adatoms are typical dipole repulsions.

Oxygen on tungsten or carbon – The attractive forces are probably typical

valence forces. That they are not ordinary Coulomb forces, such as those effective in caesium adsorption, is suggested by a consideration of the relation of the contact potential to the heat of evaporation of the adatoms. A film of caesium which has the maximum effect on the electron emission ($\Theta =$ 0.67) has a contact potential of + 3.0 volts against tungsten, while the heat of evaporation of the adatoms corresponds to 1.9 electron volts. With an oxygen film produced when a tungsten filament at 1,600° is in contact with oxygen at low pressure, the contact potential against tungsten at 1,600° is — 1.6 volts, but the heat of evaporation is about 7 volts.

The adsorption of oxygen, hydrogen and carbon monoxide on platinum[36] affords other examples of adsorption dependent on primary valence forces.

Oil films on water – In these cases the attractive forces that cause the active heads to spread over the surface are principally dipole forces between the heads and the water molecules with some contribution from Van der Waals' forces. Above the heads there is a hydrocarbon phase in which Van der Waals' forces and the repulsive forces between completed shells predominate.

Non-polar gases on glass – The adsorption of such gases as nitrogen, argon, etc. on glass or mica at low temperatures is determined by typical Van der Waals' forces[24].

Activated adsorptions

Because of the various types of adsorption that exist, a single gas may be adsorbed by a given surface in several different ways. At sufficiently low temperatures Van der Waals' forces alone would be sufficient to cause adsorption (Van der Waals' adsorption). At higher temperatures molecules on the surface may undergo chemical change and thus be held by valence forces. The heat of adsorption is then far greater than corresponds to the Van der Waals adsorption. The only reason that such adsorption does not occur at low temperatures is that the reaction velocity of the chemical change may be too low. Since there is an activation energy associated with each such reaction, H. S. Taylor[34] has proposed the term *activated adsorption* for the adsorption which involves such chemical changes.

In some cases, such as the adsorption of caesium atoms on tungsten, the adsorption involves only the transfer of one electron and can thus occur at very low temperatures so that activation is not required, and only one type of adsorption is observed.

The distinction between Van der Waals' adsorption and activated adsorption was pointed out by the writer[24] in 1918 and illustrated by the adsorption of carbon monoxide and of oxygen on platinum. At the temperature of liquid air and with a clean platinum surface in contact with carbon monoxide at a pressure of 16 baryes, the surface concentration σ of the adsorbed carbon monoxide was 3.9×10^{14} molecules cm^{-2}, but, as the temperature of the platinum gradually rose to 20°C, σ *decreased* to 1.4×10^{14} and then *increased* again to 3.9×10^{14} and remained nearly constant until 200°C had been reached. When oxygen was brought into contact with platinum at liquid air temperature, 1.5×10^{14} molecules cm^{-2} were adsorbed immediately. On raising the temperature to 20°C, σ increased very slowly (in 18 hours) to 3.0×10^{14}. At 360°C σ rose to 4.8×10^{14}. It was concluded « that at liquid-air temperature platinum adsorbs carbon monoxide in much the same way that glass does, that is, by secondary valence forces. With a moderate rise in temperature this gas is released, but in the neighborhood of room temperature the reaction velocity becomes sufficient for the platinum to react (primary valence) with the carbon monoxide to form a much more stable adsorbed film. »

In a discussion of the mechanism of the dissociation of hydrogen on tungsten filaments in 1916 the writer considered[7] the possibility that the adsorbed hydrogen exists on the surface in two forms and that the velocity of interaction between these forms may determine the rate of production of atomic hydrogen. The mathematical formulation which was given is applicable to many cases of activated adsorption.

Within recent years H. S. Taylor[34] and his co-workers have discovered many cases of activated adsorption and have demonstrated their importance in an understanding of contact catalysis. The velocity of the activation reaction, which is often low even at a temperature of several hundred degrees, has been measured and the activation energy calculated. Other investigators have sought to explain these slow surface reactions by assuming solution of the adsorbed gas in the underlying substance or slow penetration into cracks or capillary spaces.

That this cannot be a general explanation is proved by some experiments[35] that Dr. Blodgett and I have made on the thermal accommodation coefficient of hydrogen in contact with tungsten. At temperatures from 200°K to 600°K a stable adsorbed film of hydrogen on tungsten is formed which gives an accommodation coefficient α of about 0.22. As the temperature is raised, this film goes over slowly into a much more stable film which is charac-

terized by a value of $\alpha = 0.14$. The reaction velocity is such that the formation of the stable film requires several minutes at 600°K and a small fraction of a second at 900°, indicating an activation energy of the order of at least 20 kg calories per molecule. Since the accommodation coefficient is a purely surface property, these experiments prove that these two forms of hydrogen film are both monatomic films which probably represent two kinds of chemical binding by valence forces. At temperatures below liquid-air temperature a clean tungsten surface would undoubtedly show also Van der Waals' adsorption of hydrogen. This would thus be a third kind of adsorbed film of hydrogen on tungsten.

Catalytic action of surfaces

A monatomic film of oxygen on tungsten at 1,500° acts as a catalytic poison for nearly all the reactions which would otherwise occur in contact with the tungsten surface[15]. Thus the dissociation of hydrogen into atoms at 1,500°K is stopped by a trace of oxygen, as is also the decomposition of ammonia, methane, or cyanogen. The effect of the oxygen is to cover the surface so that the other gas cannot make contact with the tungsten surface.

Similarly hydrogen and carbon monoxide act as catalytic poisons on platinum surfaces[36]. The rate at which carbon monoxide and oxygen combine in contact with platinum is proportional to the pressure of oxygen and inversely proportional to the pressure of the monoxide. The reaction velocity depends on that fraction of the platinum surface which is *not covered* by adsorbed molecules of carbon monoxide. The oxygen molecules that can become adsorbed in these vacant spots and so be adsorbed on the platinum surface can thus react with adjacent adsorbed molecules of carbon monoxide.

In numerous cases investigated, the action of a surface in catalyzing a gas reaction involves just such interaction between molecules adsorbed in adjacent elementary spaces on the surface. On this basis it is possible to develop[7,13,36] a «law of mass action» for the velocity of surface reactions by which the observed reaction velocities can be explained quantitatively. It has been pointed out[15] that reactions of this sort are extremely sensitive to the actual distances between the atoms in the surface of the catalyst. Thus with many surfaces there is only a relatively small fraction of the surface on which the reaction can occur with extreme rapidity, while over the larger part of the surface it takes place at a negligible rate. A quantum theory explanation

of the importance of the spacing of the atoms in the catalyst has recently been given by Sherman and Eyring[37].

The presence of a second layer of adsorbed atoms or molecules, although this second layer may cover only a minute fraction of the surface, is often of great importance in the mechanism of gas reactions brought about by a surface catalyst.

Thus in the oxidation of heated tungsten filaments in oxygen at low pressures by which WO_3 is formed, the oxygen molecules incident on a surface already nearly completely covered by a monatomic film of oxygen atoms, condense and momentarily exist in a second adsorbed layer[29]. Although the rate of evaporation from this second layer is so high that the surface concentration is very low, the adsorbed atoms or molecules in this layer move freely over the surface and thus fill up the holes in the first layer, formed when WO_3 molecules evaporate, far faster than would otherwise be possible. These atoms in the second layer can also interact with those in the first layer and with the underlying tungsten to form the molecules of WO_3 which escape from the surface.

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Biography

Irving Langmuir was born in Brooklyn, New York, on January 31, 1881, as the third of four sons of Charles Langmuir and Sadie, *née* Comings. His early education was obtained in various schools and institutes in the U.S.A., and in Paris (1892–1895). He graduated as a metallurgical engineer from the School of Mines at Columbia University in 1903. Postgraduate work in Physical Chemistry under Nernst in Göttingen earned him the degrees of M.A. and Ph.D. in 1906.

Returning to America, Dr. Langmuir became Instructor in Chemistry at Stevens Institute of Technology, Hoboken, New Jersey, where he taught until July 1909. He then entered the Research Laboratory of the General Electric Company at Schenectady where he eventually became Associate Director.

Langmuir's studies embraced chemistry, physics, and engineering and were largely the outgrowth of studies of vacuum phenomena. In seeking the atomic and molecular mechanisms of these he investigated the properties of adsorbed films and the nature of electric discharges in high vacuum and in certain gases at low pressures.

His work on filaments in gases led directly to the invention of the gas-filled incandescent lamp and to the discovery of atomic hydrogen. He later used the latter in the development of the atomic hydrogen welding process.

He was the first to observe the very stable adsorbed monatomic films on tungsten and platinum filaments, and was able, after experiments with oil films on water, to formulate a general theory of adsorbed films. He also studied the catalytic properties of such films.

Langmuir's work on space charge effects and related phenomena led to many important technical developments which have had a profound effect on later technology.

In chemistry, his interest in reaction mechanism caused him to study structure and valence, and he contributed to the development of the Lewis theory of shared electrons.

Among the awards made to him were: Nichols Medal, (1915 and 1920);

Hughes Medal (1918); Rumford Medal (1921); Cannizzaro Prize (1925); Perkin Medal (1928); School of Mines Medal (Columbia University, 1929); Chardler Medal (1929); Willard Gibbs Medal (1930); Popular Science Monthly Award (1932); Nobel Prize in Chemistry (1932); Franklin Medal and Holly Medal (1934); John Scott Award (1937); «Modern Pioneer of Industry» (1940); Faraday Medal (1944); Mascart Medal (1950). In addition, he was a Foreign Member of the Royal Society of London, Fellow of the American Physical Society, Honorary Member of the British Institute of Metals, and of the Chemical Society (London). He had served as President of the American Chemical Society and as President of the American Association for the Advancement of Science.

Honorary degrees were bestowed upon Langmuir by the following colleges and universities: Northwestern, Union, Edinburgh (Scotland), Columbia, Kenyon, Princeton, Lehigh, Harvard, Oxford, Johns Hopkins, Rutgers, Queens (Canada), and Stevens Institute of Technology.

Dr. Langmuir's hobbies were mountaineering, skiing, flying, and, most of all, to understand the mechanism of simple and familiar natural phenomena. He married Marion Mersereau in 1912. They had a son, Kenneth, and a daughter, Barbara. After a short illness, he died on August 16, 1957.

Chemistry 1933

Prize not awarded.

Chemistry 1934

HAROLD CLAYTON UREY

«for his discovery of heavy hydrogen»

Chemistry 1934

Presentation Speech by Professor W. Palmær, Chairman of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

A short time ago a politician of prominent rank, when speaking on a festal occasion, remarked that at the present day it might appear to be an actual desideratum for the activity of the inventor in the technical field to be checked and given pause for some little time to come. That rather startling utterance was prompted by the volume of the existing unemployment and by the risk there is of that unemployment being further augmented, if technical ingenuity and skill are to continue to have free play.

In the minds of some chemists a somewhat similar chain of reasoning may be awakened, when they are brought to contemplate the particular discovery to whose originator the Royal Swedish Academy of Sciences has resolved to award the Nobel Prize for Chemistry for the current year. For the fact is, that this discovery creates serious disorder in those trains of concepts along which we have latterly been accustomed to let our thoughts range with a certain degree of composure. Instances of similar character have occurred before both in chemistry and in other sciences, but so soon as time has allowed of an adjustment to the new outlook afforded by the discovery, one will realize as a matter of course that a big step forward has been achieved, in itself a cause for gratification.

In order to throw light upon the situation we are presented with, it is incumbent on me first of all to mention what is to be understood by *isotopes*. For ever so long past, the metal copper, for instance, has always been regarded as a simple element with an atomic weight 63.6, the latter fact implying that an atom of copper weighs 63.6 times as much as the arbitrarily adopted unit for atomic weights. The said unit is no longer, as it was formerly, the exact weight of an atom of hydrogen, being actually somewhat less; but, for our present purposes, we can ignore that fact and term the atomic weight of hydrogen the unit. However, as the result of work that has been pursued from the year 1910 onwards, principally by the English investigators, Soddy and Aston, both former Nobel Chemistry Prize winners, the very remarkable circumstance has been discovered that each of certain elements, hither-

to regarded as completely homogeneous, consists as a matter of fact of an amalgamation of two or more substances with atomic weights that differ one from another but which are nevertheless from a chemical point of view, so far as has been hitherto ascertained, practically speaking identical. Aston has designed an instrument, the so-named mass spectrograph, which enables us with the aid of electrical and magnetic forces to prove the existence of these so-termed isotopes with the utmost certainty, and also to determine their respective atomic weights. Thus, it has been established that copper consists of an amalgamation of two isotopes with atomic weights of 63 and 65. An amalgamation of that character, in fitting proportions, can manifestly appear to have an intermediate atomic weight of, say, 63.6. In other instances the number of isotopes may be much larger – for tin for instance there have been shown to exist no less than eleven.

Aston discovered, however, in addition, that the atomic weights of these isotopes were always, at any rate very nearly, whole numbers, and also, as stated, that chemically no difference between the various isotopes was demonstrable; that explains how it came about that an amalgamation of them could be conceived to be a homogeneous chemical element.

The explanation, again according to the modern atomic theory, is that the chemical properties of the elements are dependent, not directly upon the magnitude of the atomic weights, but upon the number of positive, electric unit charges – consequently always of necessity a whole number – in the so-termed atomic nucleus, around which a corresponding number of free negative electricity units, the so-termed electrons, revolve like the planets round the sun.

Seeing that the isotopes had identical chemical properties, chemists accepted their discovery with tranquillity – indeed, after it had been established that the atomic weights of the isotopes were all whole numbers, with a degree of satisfaction, for thereby a justification was afforded for Prout's very attractive hypothesis, enunciated more than 100 years ago, that the atomic weights of all the elements were multiples of that of hydrogen and consequently whole numbers.

A little more than three years ago Harold C. Urey attacked the problem of finding out whether it might be possible to discover an isotope of the simplest of all the elements, viz. hydrogen. When he began that task, Urey was attached, as Assistant Professor of Chemistry, to that large and far-famed institution, the Columbia University in New York, and he advanced last spring to a full professorship there in the same subject.

As the atomic weight of hydrogen is approximately equal to 1, and as the atomic weights of the isotopes must differ by whole numbers, it follows that the nearest to ordinary hydrogen of any hydrogen isotopes there may be, must have an atomic weight of approximately 2, consequently double (100% more than) that of the hydrogen hitherto known. Now the atomic weights of hitherto known isotopes, namely those of elements with pretty large atomic weights, only differ from each other by a few units, the difference in their respective atomic weights being consequently only a few percents in isotopes of elements having large atomic weights. That might possibly be the explanation of how it is that isotopes of such elements have not shown any difference one from another in chemical respect. But how would matters stand with regard to a possible hydrogen isotope with an atomic weight 100% higher than that of the hydrogen previously known? That was the interesting question which presented itself, and the answer turned out to be, as I shall state more fully later on, that there proves to be a marked difference between the two hydrogen isotopes in chemical respect also. It is that circumstance which has perturbed chemists and roused them out of a state of mental tranquillity regarding this matter which had been induced in them, as above mentioned, by their foregoing contemplation of the isotopes.

When Urey set about his attack upon the question, it was not altogether untrodden ground, for there had been suppositions expressed as to the existence of a hydrogen isotope, a number of experiments having even been made to prove it, without however having led to any definite result. Urey proved to be the man to tackle the question in a rational way and to solve it. By the aid of modern theories he could calculate that the heavy hydrogen of mass 2 would be somewhat less volatile than the light hydrogen of mass 1, and that as a consequence it ought to be possible to a certain degree to separate the two isotopes one from another by a distillation of liquid hydrogen. For hydrogen, however, to assume the fluid form at all an exceedingly high degree of refrigeration must be attained, for the boiling point of hydrogen is round about $-250°C$. Apparatus for the production of liquid hydrogen Urey had none, and consequently he applied to a friend of his, Dr. Brickwedde of the Bureau of Standards at Washington, requesting him at his Institution, which is very finely equipped, to carry out the desired distillation of liquid hydrogen, in order to obtain the isotope sought for in concentrated form. Meanwhile, with the aid of his assistant, Dr. Murphy, Urey worked out calculations as to what would be the appearance of the spectrum of the hydrogen isotope that he was awaiting. When he then ob-

tained the expected sample it was subjected to examination by the spectroscopic method and the presence of the new isotope was established; in ordinary hydrogen it occurs in the approximate proportion of 1 to 5,000. The result was published in January 1932.

This was in itself already a matter of prime interest. Of considerably greater interest, however, is the fact that a difference in chemical respect between two isotopes became apparent here for the first time. As already stated no difference of the kind could previously been established. In this case, however, success had been achieved and thereby was affected in the first place our conception of water – of honest old water which had always been regarded as the typical example of a simple, respectable and straightforward chemical compound. The smallest particles of water, its molecules, are regarded as consisting of two atoms of hydrogen, with atomic weight 1, and one atom of oxygen, with atomic weight 16. As the whole molecule, taking the atomic weight of hydrogen as the unit, thus weights 18, water ought to consist of hydrogen to the extent of $\frac{2}{18}$ or $\frac{1}{9}$, i.e. to about 11%, the remainder being oxygen. If, however, the two hydrogen atoms are replaced by the atoms of the isotope, which are twice as heavy, the water will consist of four parts by weight of hydrogen and sixteen parts by weight of oxygen, i.e. will contain 20% of hydrogen. It should also be heavier, inasmuch as each particle is heavier in the proportion of 20 to 18.

In ordinary water both kinds of hydrogen must be present, since besides in other ways they can be obtained directly from water. The best method for separating off the heavy water from ordinary water is by electrolysing the water, i.e. by sending an electric current through water that has been rendered conductive by the addition to it for instance of caustic soda. Thereby hydrogen gas is generated at the negative pole and it is then found that the hydrogen gas given off contains proportionally a larger quantity of light hydrogen than the water itself, implying that the latter consequently becomes richer in heavy hydrogen. The original idea of adopting this method is attributable to the late Dr. E. W. Washburn, of the Bureau of Standards, Washington, who died on February 6, 1934, and the further development of the method was largely due to him too, though Urey collaborated by carrying out the spectroscopic examinations of the samples. In natural water the proportion existing between the molecules of heavy and ordinary water is approximately 1 to 5,000.

It has also proved possible to obtain heavy water in a pure form. This was accomplished first by G. N. Lewis and his co-workers, at Berkeley, Cali-

fornia (July 1933). Whereas, as we know, one litre of ordinary water weighs one kilogramme, one litre of heavy water weighs about one kilogramme and one hectogramme, which approximately corresponds to the increase in the weight of the molecule. Its freezing-point is $+3.8^{\circ}$ instead of 0° (that of ordinary water), and its boiling-point is 1.4 degrees higher than that of ordinary water. It is more viscous than ordinary water and the solubility of salts in it is less, etc., etc. It has furthermore proved possible either wholly or partially to replace by heavy hydrogen the ordinary hydrogen that is a constituent of ammonia, hydrochloric acid, acetic acid, sugar, albumen, etc., etc. As heavy and light hydrogen thus – in contradistinction to previously known isotopes – possess different chemical characteristics, it has been thought advisable to bestow on them individual names. Urey calls heavy hydrogen *deuterium* and ordinary hydrogen *protium*. The reaction velocity for ordinary hydrogen or ordinary water respectively, as compared with deuterium or heavy water respectively, has proved to differ on occasion, as has also the ultimately obtained yield of the reaction. Among chemico-biological effects there may be noted: that alcoholic fermentation proceeds more slowly in heavy than in ordinary water, that the sprouting of tobacco seeds and the evolution of yeast fungi are delayed or checked, etc., etc. Atomic nuclei of heavy hydrogen, when propelled as rapid projectiles by an electric field have proved to be exceedingly effective in the breaking down of atoms and in transformation of elements in conjunction therewith. Radio-sodium produced by that process may perhaps prove to be of medicinal importance.

These initial discoveries are undoubtedly of great importance for chemical science. Whether and in what measure they will prove capable in the near future of bringing about anything of direct practical advantage to humanity, time will show.

Urey, who was born in 1893, has already been the recipient in America of a highly valued distinction, viz. the medal that perpetuates the memory of Willard Gibbs, the author of works of the greatest moment in theoretical chemistry. On the occasion of the presentation of the medal, last spring, Urey gave a lecture, in which he vividly described the history of the discovery, stating, for instance, that the idea of concentrating the isotope that was being sought for flashed into his mind while he was attending a lunch in August 1931. He goes on to say that he had then to wait for a couple of months for the samples of hydrogen gas from Washington, and that, after their arrival he and his assistant Murphy worked at the spectroscopic investigation practically day and night for a whole month, in that way ac-

complishing work that would otherwise have demanded four months. The most trying experience they had was when, for a considerable time, they were unable definitely to determine whether the new lines that they observed in the spectrum actually proceeded from the isotope they were seeking for, or were so-termed «ghost-lines», due to minor faults in the apparatus. Just then their consumption of cigarettes increased tenfold and they were quite insufferable in association with their fellows, including even Mrs. Urey, who for the time being was left completely in the cold.

Their haste was moreover fully justified, for, as already mentioned, there had been suggestions put forward in other quarters that there should exist a hydrogen isotope. And when the discovery was revealed in January 1932, scientists everywhere, primarily in the United States, but also in European countries and in Sweden amongst others, seized upon this sensational new idea to such purpose, that the number of treatises on questions related to the matter at the present time already amounts to two hundred. In the ranks of the other investigators the late E. W. Washburn, already alluded to, should undoubtedly be placed first, for his contributions to the problem of the production of heavy water. At the present time heavy water is produced technically in many places, more especially at Rjukan in Norway, where the Norsk Hydro Concern has established a gigantic plant for the production of hydrogen by the electrolytic process. They calculate there on obtaining half a kilogramme every twenty-four hours.

The merit of having made the actual fundamental discovery appears, however, to belong mainly to Urey and hence the Academy of Sciences has resolved to award this year's Nobel Prize for Chemistry to him, in recognition of his discovery of heavy water.*

* The happy occasion of his fatherhood on Nobel Commemoration Day, and consideration for his wife, have prevented Professor Urey to be present at the Ceremony.

Harold C. Urey

Some thermodynamic properties of hydrogen and deuterium

Nobel Lecture, February 14, 1935

In the twenty-odd years which have elapsed since the existence of isotopes was first well established, isotopes of most of the chemical elements have been discovered and their individual masses determined. Of the several hundred now known, by far the majority have been revealed by Aston's mass spectrograph[11]. In recent years rare isotopes of exceptional interest have been found by the molecular spectrum method, the first being the isotopes 17 and 18 of oxygen, discovered by Giauque and Johnston[12]. Then the isotopes 15 of nitrogen and 13 of carbon, detected in studies of molecular spectra by Naudé[13] and by Birge and King[14] respectively, were added to the list of known isotopes.

Due to these discoveries the abundant isotopes of the light elements were known when the existence of the hydrogen isotope of atomic weight two, now called deuterium, was first demonstrated in 1931. Previous to the experimental detection of deuterium an empirical regularity among the known isotopes which indicated the possible existence of $^{2}H(D)$, $^{3}H(T)$ and ^{5}He had been recognized[29]. Figure 1 *a* shows this regularity in the form of a plot of the number of neutrons and protons in atomic nuclei calculated on the assumption that nuclei consist of a number of protons equal to the atomic number and of an additional number of neutrons sufficient to account for the approximate atomic weight. (This regularity was originally presented in the form of an electron–proton plot.) Though without adequate theoretical support the relationships in the plot cannot be regarded as a definite prediction of the existence of ^{2}H, ^{3}H and ^{5}He, the knowledge of them served to stimulate the search for isotopes of the lighter elements. Since 1931 the existence of ^{2}H, of ^{3}H and also of ^{3}He, which is not expected on the basis of the plot, have been revealed; ^{5}He, however, has not been detected. Figure 1 *b* shows this plot as it is now. The recently discovered unstable nuclei are not included.

The determination of the exact atomic weight of ^{1}H relative to ^{16}O, taken as the standard of atomic weights equal to 16 units, and the determination of

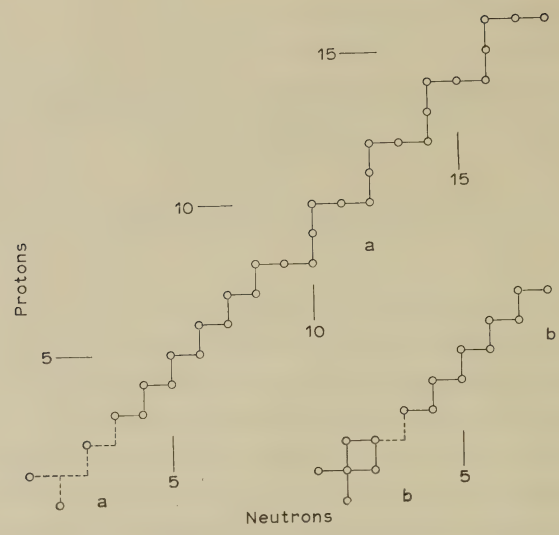

Fig. 1. (*a*) The plot of the numbers of protons and neutrons in the nuclei of the lighter elements known in 1931; (*b*) a same plot for the first few elements as of January 1935.

the chemical atomic weight of the natural mixture of the oxygen isotopes showed, as was first pointed out by Birge and Menzel[15], that a hydrogen isotope of mass 2 might be present to the extent of 1 part in 4,500 of the light variety. This was the maximum abundance that could be expected, since the presence of any heavier isotope of hydrogen would have meant that all additional isotopes must be less abundant than one part in 4,500. This estimate is based upon a difference of 2 in the fourth decimal place in atomic weights when reduced to the same standard; this is only slightly greater than a reasonable estimate of the probable error of the chemical determinations. More recent determinations of the abundance of ^{18}O necessitate a revision of this estimate to 1 : 3,700 instead of 1 : 4,500. (See Addendum, p. 354.)

In order to demonstrate the existence of such a rare isotope, it seemed to be necessary to concentrate it in some way, for no isotope so rare as this had been found by any of the methods known at that time. This was subsequently shown not to be true because of the adoption of a very sensitive method for the detection of this isotope, namely the use of the atomic spectra, which can be used in this case because of the relatively large atomic isotope effect to be expected from the theory of Bohr. However, the isotope of hydrogen of atomic weight 2, or deuterium, was concentrated by the distillation of hydrogen in order to facilitate its detection.

Previous to the carrying out of the experiments on the concentration of

this substance, calculations were made on the vapor pressures of the molecules* H_2, HD and HT, on the basis of the following postulates: (i) the internal rotational and vibrational energies of the molecules are the same in the solid and gaseous states and thus were not considered in the calculation of the vapor pressures; (ii) the free energy of the solids may be calculated from the Debye theory of the solid state: the Debye Θ''s ($= h\nu/k$) of the three solids** are inversely proportional to the square roots of the molecular weights; (iii) the free energy of the gas is given by the free energy equation for an ideal monatomic gas[16]. Further, the Θ'_{I} used in these calculations for the hydrogen molecule, H_2, was that required to describe the heat capacity of the solid hydrogen under its saturation pressure, using the Debye theory for the heat capacities of a monatomic solid. Also, it was assumed that the heats of vaporization of the hypothetical vibrationless solid hydrogen, solid hydrogen deuteride and solid hydrogen tritide to the gaseous phase are the same, in the neighbourhood of absolute zero. The vapor pressure of one of the solids on the basis of these assumptions is given by the equation:

$$\ln P = \frac{E_0}{RT} + \frac{F_s}{RT} + \ln M^{3/2}\, T^{5/2} - \frac{\chi}{RT} + \text{const.} \qquad (1)$$

where χ is the heat of vaporization of the vibrationless solid to the motionless gas at absolute zero. E_o is the zero point energy of the solid due to the Debye vibrations, and F_s is the free energy of the solid at temperature T, exclusive of the zero point energy. The vapor pressure equation depends upon the mass only through the dependence of the zero point energy and the free energy of the solid on the mass and through the dependence of the free energy of the gas on the ln M term. Hence, for the ratio of the two vapor pressures, we secure

$$\ln \frac{P(\mathrm{H_2})}{P(\mathrm{HD})} = \frac{E_0(\mathrm{H_2}) - E_0(\mathrm{HD})}{RT} + \frac{F_s(\mathrm{H_2}) - F_s(\mathrm{HD})}{RT} + \frac{3}{2} \ln \frac{M(\mathrm{H_2})}{M(\mathrm{HD})} \qquad (2)$$

Simon and Lange[17] have shown that the value of the Θ'_{I} for the hydrogen is 91 and from this the value of the Θ''s for hydrogen deuteride and hydrogen tritide are easily calculated to be 74.3 and 64.4 respectively, assuming that the molecular weights of the three molecules are in the ratio 2 : 3 : 4.

* H, D and T and the names hydrogen, deuterium and tritium are used for the atoms and substances represented by the symbols ^{1}H, ^{2}H and ^{3}H.

** The prime is used to distinguish this approximate Θ' from the true Θ used below.

The use of this simple theory gives for the ratios of vapor pressures of hydrogen to hydrogen deuteride and of hydrogen to hydrogen tritide, the values 2.23 and 3.35 respectively. Using these values for the ratio of vapor pressures, simple calculations showed that very effective concentration of deuterium should be secured by the simple distillation of solid hydrogen at the triple point. Of course, it was impossible to be certain that these differences would apply to the liquid state, but it was a reasonable postulate that at least some of the effect would persist into the liquid state.

Bohr's theory, given some twenty years ago, permits the calculation of the Balmer spectrum of the heavier isotopes of hydrogen from this spectrum of hydrogen by the well-known theoretical formula for the Rydberg constant. The value of the Rydberg constant for the hydrogen isotopes can be calculated from the atomic weights of the isotopes and the known atomic weight of the electron. The expected wavelengths of the Balmer series, using the most recent determinations for the atomic weights of hydrogen, deuterium and tritium, and of the electron, are given in Table 1.

Dr. F. G. Brickwedde, of the United States Bureau of Standards, very kindly prepared samples of hydrogen evaporated in accordance with the conditions indicated by the theory outlined above. The best sample was obtained from 4,000 cc. of liquid hydrogen which was evaporated near the triple point until a residue of approximately 1 cc. remained. My research assistant, Dr. G. M. Murphy, and I, in the fall of 1931, investigated the atomic spectrum of this sample and other samples of fractionated hydrogen as well as natural hydrogen, using a 21-ft. concave grating having 15,000 lines to the inch. We found three members of the Balmer series of deuterium even when commercial electrolytic hydrogen was used. The light of these

Table 1. Calculated wavelengths (*in vacuo*) of the Balmer lines of hydrogen, deuterium, and tritium.

	λ (H)	λ (D)	λ (T)	$\Delta\lambda$ (*calc.*) (H — D)	$\Delta\lambda$ (*obs.*) (H — D)
α	6564.686	6562.899	6562.304	1.787	1.79
β	4862.730	4861.407	4860.966	1.323	1.33
γ	4341.723	4340.541	4340.148	1.182	1.19
δ	4102.929	4101.812	4101.440	1.117	1.12

The values have been calculated by using $M_H = 1.007775$, $M_D = 2.01363$, $M_T = 3.0151$ and $m_e = 5.491 \times 10^{-4}$ and taking R_H equal to 109677.759 cm^{-1}.

wavelengths was increased by a factor of four or five times in the samples prepared by Dr. Brickwedde. Moreover, the Dα line was found in the concentrated samples and was found to be a doublet of approximately the separation required by the fine structure theory for the hydrogen lines. It was concluded that these additional lines were to be interpreted as due to the hydrogen isotope of atomic weight two, since (i) their wavelengths agreed within the experimental error of about 0.02 Å unit with the predicted theory for the wavelengths for this isotope, (ii) the Dα line was found to be a doublet as required by theory and by experiments on the hydrogen lines, (iii) these wavelengths of deuterium appeared on our plates only when the discharge was run in the so-called black stage, which produces an intense atomic spectrum, indicating that they were atomic lines and not lines of the molecular spectrum of ordinary hydrogen, and (iv) the deuterium lines were stronger in the concentrated samples, thus showing that a concentration had been effected and that the lines were not due to ghosts. Further, it was shown that there were no recorded molecular lines which agreed with the calculated and observed positions of the Dα, Dβ, Dγ and Dδ lines. The mean value of the wavelength differences for the hydrogen and deuterium lines, as observed in all the samples of hydrogen investigated at that time, are recorded in Table 1. No evidence was secured for the presence of a hydrogen isotope of atomic weight 3.

Though the deuterium line is easily detectable in the natural hydrogen, it would have been very difficult to have definitely established its existence if the more concentrated samples prepared by distillation had not been used, for irregular « ghosts » of a ruled grating might conceivably have accounted for the observed additional lines. Thus, the method of concentration devised for and used in these original researches, was important in proving the existence of this isotope[1].

The theory of hydrogen and deuterium vapor pressures

The practically complete separation of hydrogen and deuterium has permitted an investigation of the vapor pressure of pure deuterium and the direct comparison of its vapor pressures with that of hydrogen. Lewis and Hanson[18], and Scott, Brickwedde, Urey and Wahl[8] have investigated these vapor pressures experimentally. The results are in essential agreement, though they deviate from each other in a direction which could be accounted for by the

assumption that Lewis and Hanson used a less pure sample than the latter authors*.

The vapor pressure of deuterium in terms of the vapor pressure of liquid hydrogen is given by the following equations:

$$\log_{10} P(D_2 \text{ liquid}) = -1.363 + 1.310 \log P(H_2 \text{ liquid}) \quad (3)$$
$$\log_{10} P(D_2 \text{ solid}) = -1.954 + 1.534 \log P(H_2 \text{ liquid}) \quad (4)$$

Using an equation for the vapor pressure of liquid hydrogen devised by Scott, Brickwedde, Urey and Wahl, namely:

$$\log_{10} P(\text{mm of Hg}) = 4.6633 - 44.7291/T + 0.02023\ T \quad (5)$$

the equations for the vapor pressure of solid and liquid deuterium become:

$$\log_{10} P(D_2 \text{ liquid}) = 4.7459 - 58.5951/T + 0.02650\ T \quad (6)$$
$$\log_{10} P(D_2 \text{ solid}) = 5.1995 - 68.6144/T + 0.03103\ T \quad (7)$$

Equations (3) and (4) are independent of the temperature scale, since the vapor pressures of hydrogen and deuterium were compared directly, but equations (6) and (7) depend upon the temperature scale. The vapor pressures at the temperatures for which measurements were made, together with the heats of transition derived from them, are given in Table 2.

In a more exact theory of the vapor pressures of hydrogen and deuterium than that given above it is necessary to include the deviations from the ideal gas law as well as slight corrections for the free energy of the solid at varying pressures. To do this it is necessary to adopt an equation of state for deuterium, and as a first approximation we may assume that hydrogen and deuterium follow the same equation of state. The equation:

$$PV = RT\{1 - (0.0381/V)(1 + 1150/T^2)\} \quad (8)$$

is in accord with the latest experimental determinations of the virial coeffi-

* Dr. Brickwedde informs me that he has investigated samples supplied to him by Professor H. S. Taylor and found lower vapor pressures than those reported by Scott, Brickwedde, Urey and Wahl by an amount which would indicate that the samples of Professor Taylor are purer deuterium by about 0.3 percent than the ones used in the vapor pressure experiments.

Table 2.[1]

T	H_2			D_2			
	$P(H_2)$	ΔH	ΔH (*ideal*)	$P(D_2)$	[2]ΔH	[2]ΔH (*ideal*)	[3]ΔH (*ideal*)
13.92	(54)	245.7 (28.0)	247.7 [4](28.0)				
13.92	(54)	217.7	219.7	(5)	340.8	340.9	341.1
15.188	106.1			14.2	345.4	345.7	345.8
16.430	190.3			35.0	349.6	350.2	350.0
17.479	287.0			65.5	352.7	353.7	353.7
18.182	372.4			97.7	354.5	355.9	355.9
18.58	(429)	218.7	224.8	(121)	355.4 (52.3)	357.1 (52.3)	357.2 [4](52.4)
18.58	(429)			(121)	303.1	304.8	
18.945	484.9			142.4	304.0	305.9	
18.953	486.0			143.2	304.0	305.9	
19.167	521.7			157.1	304.4	306.5	
19.330	550.0			168.5	304.8	306.9	
19.969	672.0			218.5	306.0	308.6	
20.334	749.8			252.0	306.6	309.6	
20.38	760	215.9	225.3	(257)			
23.5	(1760)			(760)			

[1] The values of the vapor pressures enclosed in parentheses are interpolated or extrapolated values.

[2] ΔH recorded in this column is the heat of vaporization of deuterium in the condensed phase to the gas at the saturation pressure calculated from the empirical vapor pressure equation. ΔH (ideal) is the heat of vaporization to the gas at zero pressure.

[3] ΔH (ideal) recorded in this column is the heat of vaporization of the solid to the gas at zero pressure calculated from equation (10) using $\Theta_2' = 100$.

[4] The heats of fusion are enclosed in parentheses.

cients for hydrogen. The vapor pressure equation for solid hydrogen or deuterium then takes the form:

$$\ln P = -\frac{\Delta H_o}{RT} + \frac{5}{2}\ln T + \frac{3}{2}\ln M + 2.30259\, i + \frac{V_s P}{RT} + \frac{F_s}{RT}$$
$$+ \ln\left[1 - \frac{0.0381}{V}\left(1 + \frac{1150}{T^2}\right)\right] + \frac{2 \times 0.0381}{V}\left(1 + \frac{1150}{T^2}\right) \qquad (9)$$

where ΔH_o is the heat of vaporization at absolute zero, i is the chemical constant and is equal to —1.5882, V_s is the gram molecular volume of the solid,

F_s is the free energy of the solid at zero pressure exclusive of the zero point energy, and the other symbols have their usual significance.

Since the heat capacity of solid hydrogen under the saturation pressure can be calculated empirically by the theoretical Debye formula, using Θ_1' equal to 91, as mentioned above, the free energy F_s may be calculated from the same theory and it may be assumed that the F_s for deuterium may be calculated in a similar way, using an appropriate value for Θ_2'. By trial and error it was found that the adoption of a $\Theta_2' = 100$ gave constant values for ΔH_o, as shown in Table 3.

Table 3. ΔH_0 calculated from the vapor pressures (using $\Theta_2' = 100$).

T	15.188	16.463	17.479	18.182	
ΔH_0	276.11	275.97	276.09	276.08	Av. 276.06

In making these calculations it was necessary to compute the value of V at the pressure P from the equation of state, and then substitute its value as well as that of P in equation(9), and thus solve for ΔH_o. By this method, we find that the average value of ΔH_o in the case of deuterium is 276.0 cal per gram molecule.

Recently Bartholomé and Clusius[19] have found, from experimental determinations of the heat capacity of solid deuterium, that the Θ_2' is equal to 89, instead of 100 as deduced from the vapor pressure equation. The values of ΔH_o, using this value of Θ_2' in the vapor pressure equation, are not constant, when calculated at the four different temperatures at which vapor pressures were observed, as can be seen from Table 4.

Table 4. ΔH_0 calculated from the vapor pressures (using $\Theta_2' = 89$).

T	15.188	16.463	17.479	18.182
ΔH_0	275.33	274.96	274.89	274.72

This may mean that the equation of state for deuterium is not the same as that for hydrogen, and in fact the deviation is such that the imperfection of deuterium gas is greater than that of hydrogen gas at the same gram molecular volume. A similar effect has been noted by Rabi, who has found that the collisional areas of hydrogen and deuterium molecules are not the same for collisions with potassium and sodium atoms. Such differences are probably associated with the large differences in the internal zero point energies of these molecules.

The change in the value of ΔH_o for deuterium necessitated by the difference in equations of state, as indicated by the values given in Tables 3 and 4, does not in itself affect the conclusions which follow, though indirectly it may be important. It has been assumed that χ, the energy of separation of the molecules of the solid, is the same for hydrogen and deuterium, an assumption which must be questioned seriously, if the forces between the gaseous molecules are not the same. At present I am not able to estimate how large this difference in the χ's may be, but since the Raman frequencies of hydrogen are nearly the same in the gas and liquid this effect will probably not be very large.

Making use of the equation of state (8), the heat of vaporization is:

$$\Delta H = \Delta H_o + \frac{5}{2} RT - (RT/V)\, 0.0381\, (1 + 3450/T^2) - H_s \qquad (10)$$

H_s, the heat content of the solid under the saturation pressure, may be taken as the Debye energy with Θ_1' equal to 91 in the case of hydrogen. Using Simon and Lange's value for the heat of vaporization of solid hydrogen at the triple point, ΔH_o for hydrogen is found to be 182.9 cals per molecule.

It will be noted, first of all, that the ΔH_o's cannot be accounted for on the assumption that the heats of vaporization of the vibrationless solid hydrogen and solid deuterium are the same, and that the zero point energies have the values $9/8\ \Theta_1' R$ and $9/8\ \Theta_2' R$ since the values of Θ_1' and Θ_2' are so nearly the same. This result is to be expected, for the zero point energy of a solid should be equal to $9/8\ \Theta R$, where Θ is the Debye function $(h\nu/k)$, secured from the heat capacity at constant volume, and since the heat capacity at constant volume should be less than that at constant pressure, Θ_1 and Θ_2 should be larger than Θ_1' and Θ_2' respectively. Assuming that the heats of vaporization of the vibrationless solids are the same for hydrogen and deuterium and that the ratio of the zero point energies varies inversely as the square roots of the reduced masses, we then have the equations:

$$\chi = E_o(H_2) + 182.9 = E_o(D_2) + 276.0 \qquad (11)$$

$$E_o(H_2)/E_o(D_2) = (4.0273/2.0156)^{1/2} \qquad (12)$$

From these equations we find that $\chi = 501.2$, $E_0\ (H_2) = 318.3$ and $E_0(D_2) = = 225.2$. The corresponding Θ's are $\Theta_1 = 142.4$ and $\Theta_2 = 100.7$. These Θ's should be used to calculate the heat capacities and other thermodynamic

properties at constant volume. The striking thing about these results is that, whereas Θ_I and Θ_I' are markedly different, being 142.4 and 91 respectively, Θ_2 and Θ_2' are nearly the same, being 100.7 and 100 (or, using Bartholomé and Clusius' value, 89) respectively. This shows that the heat capacities at constant pressure and constant volume are markedly different for hydrogen but nearly the same for deuterium, and since $C_P - C_V = \alpha^2 VT/\beta$, where α and β are the coefficients of thermal expansion and compressibility respectively it follows that the ratio α^2/β must be smaller in the case of deuterium than in the case of hydrogen.

It should be noted that the zero point energy of hydrogen is about 64 per cent of the value of χ, while for deuterium it is 46 per cent of this quantity. Thus it seems probable that the oscillators for both hydrogen and deuterium which are responsible for the heat capacity are markedly anharmonic. Moreover, the oscillators of hydrogen should be considerably more anharmonic in character than those of deuterium, and hence the coefficient of expansion of hydrogen should be considerably greater than that of deuterium. This indicates that the heat capacities of hydrogen at constant volume and at constant pressure should differ more than these heat capacities for deuterium, which is in agreement with the observation. Moreover, the observation of Bartholomé and Clusius[19] that the gram molecular volume of solid hydrogen is some 11 per cent greater than that of deuterium is in agreement with this view. This difference is to be regarded as due to the greater amplitudes of oscillation in solid hydrogen and their greater anharmonic character, and this difference in gram molecular volume should persist to the absolute zero, as was observed by these authors.*

Throughout this calculation it has been assumed that the molecules of hydrogen and deuterium rotate freely in the solid state, and that the internal vibrational zero point energy is the same in the condensed and gaseous phases. It is well known that the rotational energy in the solid state is not exactly the same as that of the gaseous state, since the heat capacity of ortho hydrogen below 11° absolute is markedly different from that of para hydrogen in this temperature range. The difference can be accounted for qualitatively by assuming a simple potential energy function for rotation in the solid state. A consideration of the differences in rotational states to be expected in the case of hydrogen and deuterium indicates that no large correc-

* Clusius and Bartholomé have independently come to similar conclusions to those expressed here. (Gesellschaft der Wissenschaften zu Göttingen. Mathematisch-Physikalische Klasse, Fachgruppe III, p. 29.)

tion to the theory given above needs to be made on this ground. Studies on the Raman effect of liquid hydrogen indicate that the vibrational energy levels are not greatly perturbed in this phase. This indicates that the assumption of equal χ's for these two solids should be approximately correct and that the calculations of zero point energies and Θ's and thermodynamic properties at constant volume are a good first approximation.

From the vapor pressure data, it is also possible to conclude that the heat capacity of deuterium in the liquid state is much lower than that of hydrogen in the liquid state, though the equation of state assumed for deuterium affects the calculated values more in the case of the liquid than in that of the solid because of the higher vapor pressures.

The vapor pressures of hydrogen deuteride have not been investigated as yet because of the difficulty of preparing this molecule in the pure state. It is not at all certain that one can calculate the vapor pressure from the data on hydrogen and deuterium using the theory outlined above. The rotational states of the HD molecule in the solid state may be considerably different from those of H_2 and D_2, since rotation occurs about the center of mass which is the mid point between the nuclei in the case of H_2 and D_2 but not in the case of HD. The rotational energy might enter in an important way in this case. However, if we assume that the χ for the mixed molecule is about the same as that for the hydrogen and deuterium molecules, and that its Θ is equal to $\sqrt{\frac{2}{3}\Theta_1}$, the vapor pressure ratio of solid hydrogen and solid hydrogen deuteride at the triple point is found to be approximately 2.42.

Using this ratio in the Rayleigh distillation formula, it is possible to calculate what the increased concentration should have been in the original distillation of liquid hydrogen as carried out by Dr. Brickwedde. The hydrogen used in this distillation was prepared by electrolysis of ordinary water and, as we know now, the gas delivered from such a cell contains a smaller fraction of deuterium than does the water within the cell. It seems probable that the liquid hydrogen used contained about one part in 25,000 of deuterium. The ratio of the original to the final volume was about 4,000 and hence the concentration of deuterium should have been increased approximately 125 times instead of about 25, as actually observed. Or, if the observed fractionation factor is calculated by using one part in 25,000 for the original concentration and one part in 1,100 for the final concentration, one finds that this factor was 2.1 instead of 2.42 as required by the theory. It appears, therefore, that the enrichment secured was about what could be expected from the theory considering the difficulties of distilling liquid hydrogen.

The equilibria of exchange reactions involving hydrogen and deuterium

The equilibrium constants of exchange reactions of the general type, $AH + BD = AD + BH$, can be calculated in the case of diatomic molecules, providing the rotational and vibrational energy levels are known from molecular spectra. The theory of molecular spectra is now so well developed that a knowledge of these levels for the molecules containing hydrogen enables us to calculate these levels for the molecules containing deuterium. The standard free energy of a gas is given by the equation:

$$F^\circ = -RT \ln M^{3/2} T^{5/2} Q P^{-1} + 7.2646T + E^\circ (P = 1) \qquad (13)$$

Q is the summation of state and equals $\Sigma p \exp(-E/kT)$, E being the energy of the molecule in a steady state relative to the lowest energy level and the summation being extended over all the steady states; E° is the zero point energy per gram molecule. The equilibrium constant of the typical reaction then becomes:

$$\ln K = -\frac{E^\circ}{RT} + \ln \left[\frac{M_{AD}\, M_{BH}}{M_{AH}\, M_{BD}}\right]^{3/2} \frac{Q_{AD}\, Q_{BH}}{Q_{AH}\, Q_{BD}} \qquad (14)$$

The appropriate expressions for other exchange reactions are easily derived.

Rittenberg and I have used this theory to show that easily detectable differences in the equilibrium constants of reactions involving hydrogen and deuterium should exist, and subsequent experimental work confirmed these calculations in the case of the reaction of hydrogen and deuterium with iodine to give hydrogen iodide and deuterium iodide. This confirmation was confidently to be expected, but this seems to have been the first time that an equilibrium constant of a chemical reaction had been calculated before one of the elements involved had been prepared in sufficient quantities to confirm the theory.

The equilibrium constants calculated for the reactions

$$\begin{aligned} H_2 + 2\,DCl &= D_2 + 2\,HCl \\ H_2 + 2\,DI &= D_2 + 2\,HI \\ H_2 + D_2 &= 2HD \end{aligned}$$

are given in Table 5 for a number of temperatures. Table 6 gives the ex-

perimental values for the percentage dissociation for mixtures of hydrogen and deuterium iodide of the composition shown in column 2. The constants

Table 5. Calculated equilibrium constants of exchange reactions.[4,5,20]

T (°C)	$H_2 + D_2 = 2\,HD$	$H_2 + 2\,DCl = D_2 + 2\,HCl$	$H_2 + 2\,DI = D_2 + 2\,HI$
0	0	0	0
50	1.345		
100	2.265		
200	2.903	0.309	
298.1	3.269	0.502	1.164
400	3.494	0.647	1.212
575	3.710	0.807	1.234
700	3.800	0.874	1.222

Table 6. The dissociation of hydrogen iodide and deuterium iodide.[6]

T (°C)	*Conc. of* D	*Percent dissociation*		*Difference*	
		Exp.	*Calc.*	*Exp.*	*Calc.*
398	0.0	[3]20.72	(20.72)	0	0
398	[1]14.3	20.84	20.89	0.12	0.175
468	0.0	[3]22.72	(22.72)	0	0
468	[1]41.7	23.29	23.33	0.57	0.602
468	[2]75.5	23.88	23.94	1.16	1.222

[1] Concentration of deuterium in the hydrogen iodide – deuterium iodide used.
[2] Concentration of deuterium in the hydrogen-deuterium gas at equilibrium.
[3] Bodenstein's value for 398° C is 20.70 and at 468° C, 22.77.

for the last reaction given above have been confirmed very beautifully by Gould, Bleakney and Taylor[20].

In the original work various values for the spin of the deuteron were used and the Bose-Einstein and Fermi-Dirac statistics were considered. The first two values of column 2 are dependent on the spin and statistics, though all other values are independent of these. A spin of 1 and the Bose-Einstein statistics are used in the calculation of the constants recorded here.

Calculations of a similar kind have been made by others (Farkas and Farkas[21], Crist and Dalin[22], Topley and Eyring[23]) and these have been confirmed experimentally. It is, of course, to be expected that similar deviations from the equilibrium constants computed on the assumption of a simple statistical

distribution of hydrogen and of deuterium atoms between their compounds in condensed phases will occur, though the calculations cannot be made exactly in these cases.

The differences in vapor pressure of compounds of hydrogen and deuterium observed by Lewis and his co-workers[26,27] and others, cannot be accounted for by the theory presented above for the differences in vapor pressures of hydrogen and deuterium. If the heat capacity due to the Debye vibrations of a solid is nearly equal to the Dulong and Petit value, no differences in vapor pressures of isotopic substances can be expected from the contribution of these vibrations to the free energy. The differences in vapor pressures of these substances, such as water, ammonia, etc., must be related to the equilibria considered in this section, the differences being due to differences in zero point energies, distribution functions, etc., in the gaseous and condensed phases. At present we have no satisfactory theory for such vapor pressure differences.

The separation of isotopes

The extensive researches which have been carried out with the use of deuterium in the last two years were made possible in a large part by the discovery by Washburn[3] of the electrolytic method for the separation of hydrogen and deuterium. Other methods could be used at the present time for the separation of these isotopes. The exchange reaction between water and hydrogen could probably be adapted to counter-current scrubbing methods, and could be used effectively for the separation of the hydrogen isotopes as suggested by Farkas.

A major problem which challenges chemistry and physics today is the separation of the isotopes of the lighter elements. Orienting experiments have been made in this direction by Lewis and Cornish[24], who discovered a difference in the vapor pressures of the two waters $H_2{}^{16}O$ and $H_2{}^{18}O$, and by Hertz[28] using his ingenious diffusion apparatus.

The beautiful confirmation of the theoretical calculation in the case of exchange reactions involving hydrogen and deuterium encourages us to apply the same sort of calculation to exchange reactions involving the isotopes of other elements. Recently such calculations have been made by Dr. L. Greiff and myself[25] for a number of such exchange reactions. In the case of the exchange reaction with respect to ^{16}O and ^{18}O between water and CO_2, it is

found that the ratio of ^{18}O to ^{16}O in the CO_2 in equilibrium with water is increased by approximately 5 per cent over that of the water, and this result has been confirmed experimentally. The ratio of ^{13}C to ^{12}C in CO_2 in equilibrium with CO with respect to the carbon isotopes is about 8 or 9 per cent greater than this ratio in the CO. The isotopic composition of chlorine in equilibrium with hydrogen chloride is sufficiently different to affect the atomic weight of chlorine in the third decimal place. In general, exchange reactions for the lighter isotopes have equilibrium constants sufficiently different from unity, so that the ratios of concentrations of the isotopes in two compounds which are in equilibrium differ by a few per cents in nearly all cases. Some reactions of this kind can be adapted to counter-current scrubbing processes, using apparatus similar to fractionation columns. I believe that these calculations indicate that it will be possible to separate the isotopes of the lighter elements in considerable quantities by the use of these equilibria, though it may be that even better methods will be developed.

The discovery of deuterium and the marked differences in the physical and chemical properties of hydrogen and deuterium, together with an efficient method for the separation of these isotopes, have opened an interesting field of research in several of the major branches of science. It is my expectation that the next few years will witness the separation of the isotopes of the lighter elements in sufficient quantities for effective research in chemistry, physics and biology. If this can be effected, the work on deuterium is only the beginning of a very interesting scientific development.

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Addendum

Since this was written, Aston has revised his mass-spectrographic atomic weight of hydrogen (H) to 1.0081 instead of 1.0078 [F. W. Aston, *Nature*, 135 (1935) 541]. With this mass for hydrogen, the argument by Birge and Menzel is invalid. However, I prefer to allow the argument of this paragraph to stand, even though it now appears incorrect, because this prediction was of importance in the discovery of deuterium. Without it, it is probable that we would not have made a search for it and the discovery of deuterium might have been delayed for some time.

Biography

Harold Clayton Urey was born in Walkerton, Indiana, on April 29, 1893, as the son of the Rev. Samuel Clayton Urey and Cora Rebecca Reinsehl, and grandson of pioneers who settled in Indiana. His early education in rural schools led to his graduation from high school in 1911 after which he taught for three years in country schools. In 1914 he entered the University of Montana and received his Bachelor of Science degree in zoology in 1917. He spent two years as a research chemist in industry before returning to Montana as an instructor in chemistry. In 1921 he entered the University of California to work under Professor Lewis and he was awarded the degree of Ph.D. in chemistry in 1923. He spent the following year in Copenhagen at Professor Niels Bohr's Institute for Theoretical Physics as American-Scandinavian Foundation Fellow to Denmark and on his return to the United States he became an Associate in Chemistry at Johns Hopkins University. In 1929 he was appointed Associate Professor in Chemistry at Columbia University and he became Professor in 1934; during the period 1940–1945 he was also Director of War Research, Atomic Bomb Project, Columbia University. He moved to the Institute for Nuclear Studies, University of Chicago in 1945 as Distinguished Service Professor of Chemistry and became Martin A. Ryerson Professor in 1952. He was George Eastman Visiting Professor, University of Oxford, during 1956–1957 and in 1958 he took his present post as Professor-at-Large, University of California.

Professor's Urey's early researches concerned the entropy of diatomic gases and problems of atomic structure, absorption spectra and the structure of molecules. In 1931 he devised a method for the concentration of any possible heavy hydrogen isotopes by the fractional distillation of liquid hydrogen: this led to the discovery of deuterium. Together with the late Dr. E. W. Washburn, he evolved the electrolytic method for the separation of hydrogen isotopes and he carried out thorough investigations of their properties, in particular the vapour pressure of hydrogen and deuterium, and the equilibrium constants of exchange reactions. He later worked on the separation of uranium isotopes and, more recently, he has been concerned with the

measurement of paleotemperatures, investigations into the origin of the planets, and the chemical problems of the origin of the earth.

He is the author of the books *Atoms, Molecules and Quanta* (1930, with A. E. Ruark), and *The Planets*(1952). He was editor of the *Journal of Chemical Physics* during 1933–1940 and he has written numerous papers on the structure of atoms and molecules, the discovery of heavy hydrogen and its properties, separation of isotopes, measurement of paleotemperatures and the origin of planets. These have been published in many different chemical journals.

Professor Urey received the Willard Gibbs Medal (American Chemical Society) in 1934; Davy Medal (Royal Society, London), 1940; Franklin Medal, 1943; Medal for Merit, 1946; Cordoza Award, 1954; Honor Scroll Award (American Institute of Chemists), 1954; Joseph Priestley Award, 1955; Alexander Hamilton Award, 1961; and the J. Lawrence Smith Award (National Academy of Sciences), 1962. He has received honorary Doctor of Science degrees of Montana, Princeton, Newark, Columbia, Oxford, Washington and Lee, McMaster, Yale, Indiana, Birmingham Universities, and of the Universities of Athens, Durham, and Saskatchewan; also honorary Doctor of Law degree from Wayne University and the University of California. He is a member of many of the more important scientific societies of the world, and is Honorary Fellow of the Chemical Society (London), the National Institute of Sciences of India and the Weizmann Institute of Science (Israel).

In 1926 he married Frieda Daum. They have three daughters and one son.

Chemistry 1935

JEAN FRÉDÉRIC JOLIOT

IRÈNE JOLIOT-CURIE

«*in recognition of their synthesis of new radioactive elements*»

Chemistry 1935

Presentation Speech by Professor W. Palmær, Chairman of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

On the 10th of December, 1911, Marie Sklodowska, a Polish chemist of world-wide reputation, wife of Professor Pierre Curie, was present at the solemn Swedish Nobel Prize ceremony to receive the Prize for Chemistry «in recognition of her services to the advancement of chemistry by the discovery of the elements radium and polonium, by the isolation of radium and the study of the nature and compounds of this remarkable element.» Previously, in 1903, she had received, jointly with Professor Pierre Curie, half of the Nobel Prize in Physics «in recognition of the extra ordinary services they have rendered by their joint researches on the radiation phenomena discovered by Professor Henri Becquerel», whilst the other half of the prize was simultaneously awarded to Professor Becquerel «in recognition of the extraordinary services he has rendered by his discovery of spontaneous radioactivity».

It is evident that in 1903 it was the importance to physics of the discoveries made which was the prime consideration. However, their extraordinary importance in chemistry became increasingly clear, in the main from the work of Marie Sklodowska-Curie, but also from that of Pierre Curie while he was alive, and it was considered fitting to award Madame Curie by an undivided Nobel Prize for Chemistry–her husband had died in the meantime so that his share in their work could no longer be rewarded. This prize was duly presented in 1911, and Marie Sklodowska-Curie thereby became the only person up to that time to have received more than one Nobel Prize.

The capital importance of these discoveries is generally recognized and two other Nobel Prizes in Chemistry have been awarded for discoveries in the field of radioactive substances, in 1908 to Lord Rutherford and in 1922 to Frederick Soddy. I need only recall the powerful remedy that radium has become in medicine in the struggle against the cancerous diseases, the fact that it has proved possible to calculate the minimum age of the earth through the transformation of radioactive substances, and that we have been able to

form an idea of the internal energy of atoms, of the possibility of using radioactive substances as tracers, as they are called (a question to which I will return later), and so on. What is more interesting from the scientific point of view is that radium is spontaneously derived from uranium and that afterwards by its spontaneous and continuous disintegration it forms new elements, with lead as the final product. All these transformations are accompanied by radiations of different kinds and thus all the radioactive elements are unstable, although in different degrees. It is customary to define their stability by giving the time taken for them to become half-decomposed, a period which can be determined by observing how the intensity of the radiation diminishes. This time, which is generally known as the «half-life» can vary between thousands of millions of years (for uranium) down to fractions of a second, and the determination of this period thus forms a major means of defining the different radioactive elements. At first, three series of these were known, of which two originated from uranium, which is found as an oxide in the mineral pitchblende, and the remaining one from thorium, a metal belonging to the metals of the rare earths and whose oxide is used in the now almost obsolete incandescent mantle for gas lighting. The total number of these radioactive elements known in the early stages and formed spontaneously amounted to just over forty.

As we know, the alchemists strove to transform the elements one into another. Strictly speaking it was only one transformation of this kind which interested them, the transformation of base metals into gold and they were thus moved by purely venal motives. Yet it cannot be said that the formation of new elements in the way described above provides the solution to the alchemists' problem, for the radioactive elements known earlier appear and decompose spontaneously without it being possible in any way to interfere in the process, and a particular element cannot be transformed into another one by any artificial interference.

It is in this respect that something new has been given to science by the discoveries of Doctors Irène Joliot-Curie and Frédéric Joliot, today's Nobel Prize winners. Yet even this time it is not a question of the transformation of other metals into gold – unless it be indirectly in the form of a Nobel Prize! But it does concern the extremely interesting discovery that it is possible in certain other cases to transform one element into another by some external interference. I shall now try to give an outline of these discoveries.

The spontaneous decomposition of a radioactive element can be compared to an explosion, the radiation which is involved in it consisting of the pro-

jection at high speed of particles charged with electricity. One type of these particles, the so-called alpha particles, consists of helium atoms with positive electrical charges. I must also recall that according to the now generally accepted view an atom is composed of a nucleus with a positive electrical charge surrounded by a group of units of negative electricity, the electrons, which can be compared to a kind of planetary system round the nucleus. If an alpha particle thus thrown out happens to strike such a nucleus, which is now thought to be composed of a definite number of hydrogen nuclei with positive charges, the so-called protons, and of an equally definite number of neutrons (already mentioned this evening) – that is to say, composed of the two kinds of matter which, with the electrons, are at present considered to be the smallest stones with which the universe is built – then it may happen that the nucleus is shattered, a process by which atoms of other elements are formed.

However, the nucleus is extremely small, so small that the surface area of its cross-section forms only about one hundred-thousandth part of the whole atom with its envelope of electrons. This means that the number of effective collisions during a bombardment is minute – it is calculated that one hit occurs in ten million shots, that is out of ten million alpha particles.

So the scientific couple Curie-Joliot bombarded aluminium with alpha particles derived from polonium. Polonium, which is somewhat akin to sulphur, is a radioactive element less stable than radium and therefore it projects alpha particles in greater numbers and at higher speeds than the same amount of radium, that is, it yields a more effective radiation for atomic bombardment. As it is also among the few radioactive elements obtainable in reasonable quantity, it represents a good choice for this purpose.

Having thus exposed aluminium to bombardment, today's prize-winners found that after some minutes had elapsed the metal began to emit rays to a noticeable degree – in this case units of positive electricity, called positrons, discovered in the autumn of 1932 by Carl Anderson at Pasadena. This was an indication of the formation of a new radioactive element. And after ceasing the bombardment, the emission of rays from the aluminium did not stop immediately but continued for a while to a noticeable degree until the radioactive element created was once more for the most part decomposed in the usual manner. This was again an indication of the formation of a new radioactive element.

More extensive investigation has shown that the newly formed element is phosphorus in a new radioactive state, radio-phosphorus. This is an isotope

of ordinary phosphorus, that is, its nucleus contains as many positive charges as normal phosphorus, but its weight is different.

We have earlier indicated that, on account of their instability, it has been impossible to obtain the unstable radioactive elements, which form the majority, in reasonable quantities, so that it has been impossible to examine them or even to demonstrate their existence by chemical tests. In order to show that they exist and determine their characteristics, it is necessary to have recourse to the radiation emitted as I have previously stated. In this particular case recognition by a chemical method was successful in that it was possible to show that following the decomposition of irradiated aluminium in an acid, all the radioactivity was attached to the gas generated, which is as would be expected if an isotope of phosphorus had been formed, since gaseous phosphorus hydride would be produced. Another chemical treatment of irradiated aluminium confirmed this hypothesis.

In a similar way a new radio-nitrogen has been obtained from boron, a constituent of boric acid, and radio-silicon and radio-aluminium derived from two isotopes of the metal magnesium.

In fact it is not the first time that the transformation of one element into another by alpha-ray bombardment has been achieved, for Lord Rutherford and others had by this means succeeded in smashing the atoms of several elements, a process by which, however, the elements formed were not *new*. One can thus characterize the discovery of the couple Curie-Joliot as the *synthesis* of new radioactive elements, even though the term «synthesis» properly signifies the associating or combining into a unity, and that previously the word was only used to indicate the preparation of complex chemical compounds using simpler ones or elements as the starting-point.

The field of investigation with which we are concerned today is the object of intense activity and so the discovery of the Curie-Joliot's, communicated to the French Academy of Sciences on the 15th of January, 1934, was not long in stimulating other scientists to take up this research. It must here be emphasized that in the early stages, that is in April, 1934, the Curie-Joliot's had suggested that projectiles suitable for the disintegration of atoms were protons, deuterons (equivalent to protons but coming from heavy hydrogen, the discovery of which was rewarded last year by a Nobel Prize in Chemistry), and neutrons. With Preiswerk they themselves used neutrons but it is above all the Italian Fermi, who had already used them with great success a little before the suggestion of the Curie-Joliot's, and had arrived at a large number of extremely interesting results.

But it is the first step which counts, as an eminent scientist has rightly said in the letter in which he proposes the Curie-Joliot's for the award of this year's Nobel Prize for Chemistry.

There is hardly any need for me to add more on the importance of their discovery to science. I simply want to recall that the English scientist Boyle, to whom chemistry as much as physics owes fundamental laws, in defining the notion of a chemical element 250 years ago and in adopting for it the idea of the Greek philosopher Democritus on the indivisible atom, taught in 500 B.C., nevertheless made a wise reservation. In fact he said that perhaps someday it would be possible to find an *agens subtile et potens*, that is a subtle and powerful means, by whose aid elements might be decomposed. That vision into the future is now realized by the discoveries of this year's Nobel Prize winners for Chemistry and by those of other scientists.

Have we by this reached the end of what might be called the world of the infinitely small? Who knows, it is hardly likely. In fact, it makes us, as we think about it, as dizzy in seeking to penetrate to the bottom of what is infinitely small as it does to make out the summit of that which is infinitely large.

But it is also possible even now to get a glimpse of practical uses. Some of these artificial radioactive elements–for whose production the raw materials, the ordinary elements, that is, are available in large quantities compared with the minerals which in the earlier stages were the sources of the radioactive elements–emit a radiation known as gamma, a kind of X-rays, with a definite wavelength, which is valuable for many purposes. Again, in general the radioactive elements can only be obtained in small quantities; but on the other hand the method of determining their characteristics and their amount by observing their capacity for making, by virtue of their radiation, air or other gases into conductors of electricity, is so sensitive that it surpasses all chemical methods. On this property is based the use of radioactive elements as tracers–a method first described by de Hevesy and Paneth. The Curie-Joliot's have expressed the hope of being able very soon to supply the physiologists with radioactive preparations, containing, for example, radioactive carbon which after being introduced into the body of an animal or plant makes it possible to discover the movement and distribution of certain of the substances in the organism. And referring to radio-sodium in particular, obtained by Lawrence by bombarding sodium with deuterons, which has a sufficiently long life, it is to be hoped that it can be used in the same way as radium salts in medical applications. Here also new effects can

be expected because of the difference of radium from the chemical point of view and because no radioactive residue is formed on the decay of the new radioactive elements.

Therefore the Royal Academy of Sciences has had no hesitation in rewarding with the Nobel Prize for Chemistry the discovery which I have sought to summarize; and in doing so the Academy has also had the pleasure of being able to reward a discovery made at a quite recent date, in complete accordance with the words of Nobel's will – something which does not happen very often.

The Royal Academy of Sciences has therefore decided that the Nobel Prize for Chemistry for this year should be shared equally by the Doctors Irène Joliot-Curie and Frédéric Joliot of Paris for their synthesis of new radioactive elements carried out in partnership.

Madame, Sir. In awarding to both of you in equal shares the Nobel Prize in Chemistry for this year, the Royal Academy of Sciences has been pleased to be able to reward, in a brilliant way, the synthesis, achieved by your united efforts, of new radioactive elements.

Thanks to your discoveries, it has become possible, for the first time, to transform artificially one element into another hitherto unknown. At last the old dream of the alchemists has become reality. Their main object, the production of gold, has been attained, though by a path, it is true, less direct than they thought would lead them there. The results of your researches are of capital importance for pure science, but in addition, physiologists, doctors, and the whole of suffering humanity hope to gain from your discoveries, remedies of inestimable value.

Madame, 24 years ago, your mother, Madame Marie Sklodowska-Curie, was present at the Nobel festival in order to receive the Chemistry Prize, as a reward for her discovery of radium in the first place; and you, Madame, were also present on that occasion, as a little girl.

Her husband, your father Pierre Curie, was already dead; but earlier on, in 1903, he had shared with her, half the Physics Prize, an award well deserved for their work on the phenomena of radiation. In collaboration with your husband, you have worthily maintained those brilliant traditions. The work of both of you, Madame and Sir, has quickly attracted the attention of the scientific world, and its importance has been amply and universally recognized.

Madame Joliot-Curie, Monsieur Joliot. I ask you now to receive the prize which has been awarded to you, from the hands of His Majesty the King, who has graciously consented to present it to you.

Irène Joliot-Curie

Artificial production of radioactive elements

Nobel Lecture, December 12, 1935

It is a great honour and a great pleasure to us that the Swedish Academy of Sciences has awarded us the Nobel Prize for our work on the synthesis of radio-elements, after having presented it to Pierre and Marie Curie in 1903, and to Marie Curie in 1911, for the discovery of the radio-elements.

I would like here to recall the extraordinary development of radioactivity, this new science which had its origin, less than forty years ago in the work of Henri Becquerel and of Pierre and Marie Curie.

It is known that the efforts of chemists of the last century established as a fundamental fact the extreme solidity of the atomic structures which go to make up the ninety-two known chemical species. With the discovery of the radio-elements, physicists found themselves for the first time confronted with strange substances, minute generators of radiation endowed with an enormous concentration of energy; alpha rays, positively charged helium atoms, beta rays, negatively charged electrons, both possessed of a kinetic energy which it would be impossible to communicate to them by human agency, and finally, gamma rays, akin to very penetrating X-rays. Chemists had no less astonishment as they recognized in these radioactive bodies, elements which had undergone modifications of the atomic structure which had been thought unalterable.

Each emission of an alpha or beta ray accompanies the transmutation of an atom; the energy communicated to these rays comes from inside the atom. As long as they continue to exist, radio-elements have well-defined chemical properties, like those of ordinary elements. These unstable atoms disintegrate spontaneously, some very quickly, others very slowly, but in accordance with unchanging laws which it has never been possible to interfere with. The time necessary for the disappearance of half the atoms, called the half-life, is a fundamental characteristic of each radio-element; according to the substance the value of the half-life varies between a fraction of a second and millions of years.

The discovery of radio-elements has had immense consequences in the knowledge of the structure of matter; the study of the materials themselves,

and the study of the powerful effects produced on atoms by the rays they emit occupy scientific workers of numerous great research institutes in all countries.

Nevertheless, radioactivity remained a property exclusively associated with some thirty substances existing naturally. The artificial creation of radio-elements opens a new field to the science of radioactivity and so provides an extension of the work of Pierre and Marie Curie.

After the discovery of the spontaneous transmutations of radio-elements, the achievement of the first artificial transmutations is due to Lord Rutherford. Fifteen years later, by bombarding with alpha rays certain of the lighter atoms, nitrogen and aluminium for example, Lord Rutherford demonstrated the ejection of protons, or positively charged hydrogen nuclei; this hydrogen came from the bombarded atoms themselves: it was the result of a transmutation. The nature of the nuclear transformation could be firmly established: the aluminium atom, for example, captures the alpha particle and is transformed, after expelling the proton, into an atom of silicon. The amount of matter transformed cannot be weighed and the study of radiation alone has led to these conclusions.

In the course of recent years various artificial transmutations of different types have been discovered; some are produced by alpha rays, others by protons or deuterons, hydrogen nuclei of weight 1 or 2, others by neutrons, neutral particles of weight 1 about which Professor Chadwick has just spoken. The particles expelled when the atom explodes are protons, alpha rays or neutrons.

These transformations constitute true chemical reactions which act upon the innermost structure of the atom, the nucleus. They can be represented by simple formulae as Monsieur Joliot will be telling you in a moment.

I shall now speak to you of the experiments which have led us to obtain by transmutation new radioactive elements. These experiments have been made together by Monsieur Joliot and me, and the way in which we have divided this lecture between us is a matter of pure convenience.

In our study of the transmutations with emission of neutrons produced in the light elements irradiated with alpha rays, we have noticed some difficulties in interpretation in the emission of neutrons by fluorine, sodium, and aluminium. Aluminium can be transformed, by the capture of an alpha particle and the emission of a proton, into a stable silicon atom. On the other hand, if a neutron is emitted the product of the reaction is not a known atom.

Later on, we observed that aluminium and boron, when irradiated by alpha rays do not emit protons and neutrons alone, there is also an emission of positive electrons. We have assumed in this case that the emission of the neutron and the positive electron occurs simultaneously, instead of the emission of a proton; the atom remaining must be the same in the two cases.

It was at the beginning of 1934, while working on the emission of these positive electrons that we noticed a fundamental difference between that transmutation and all the others so far produced; all the reactions of nuclear chemistry induced were instantaneous phenomena, explosions. But the positive electrons produced by aluminium under the action of a source of alpha rays continue to be emitted for some time after removal of the source. The number of electrons emitted decreases by half in three minutes.

Here, therefore, we have a true radioactivity which is made evident by the emission of positive electrons.

We have shown that it is possible to create a radioactivity characterized by the emission of positive or negative electrons in boron and magnesium, by bombardment with alpha rays. These artificial radio-elements behave in all respects like the natural radio-elements.

Returning to our hypothesis concerning the transformation of the aluminium nucleus into a silicon nucleus, we have supposed that the phenomenon takes place in two stages: first there is the capture of the alpha particle and the instantaneous expulsion of the neutron, with the formation of a radioactive atom which is an isotope of phosphorus of atomic weight 30, while the stable phosphorus atom has an atomic weight of 31. Next, this unstable atom, this new radio-element which we have called « radio-phosphorus » decomposes exponentially with a half-life of three minutes.

We have interpreted in the same way the production of radioactive elements in boron and magnesium; in the first an unstable nitrogen with a half-life of 11 minutes is produced, and in the second, unstable isotopes of silicon and aluminium.

Frédéric Joliot

Chemical evidence of the transmutation of elements

Nobel Lecture, December 12, 1935

The interpretation of our first experiments was founded, as Madame Joliot-Curie has just explained, on facts of a purely physical order. We have considered the possibility, by using the methods of radiochemistry, of substantiating our hypotheses of providing a chemical proof of the reality of the transmutations brought about.

The first unquestionable proofs of the transformation of elements into different chemical elements have been provided by the study of the phenomena of radioactivity. There is no doubt that radium is transformed spontaneously into an active gas, radon, emitting at the same time alpha particles, or helions. We may write with certainty the corresponding nuclear reaction*

$$^{226}_{88}\mathrm{Ra} \rightarrow {}^{222}_{86}\mathrm{Rn} + {}^{4}_{2}\mathrm{He}$$

for the quantities of the various elements taking part in this reaction can be considered sufficient for their successful identification chemically and spectroscopically.

The succession of radioactive transformations provides numerous examples in which the quantities of radio-elements are extremely small and not capable of being weighed, yet nevertheless, by the methods of radiochemistry it has been possible to examine correctly their chemical properties, and identify some of them as being isotopes of elements, active or inactive, available in large quantities.

This special kind of chemistry in which one handles unweighable quantities, sometimes of the order of 10^{-16} g, is made possible thanks to the fact that one can determine and follow by measuring the radiation emitted, infinitesimal traces of radioactive matter dispersed in the midst of other matter.

But while it is possible to write with certainty the nuclear reactions cor-

* The atomic weight is placed above and to the left of the chemical symbol, and the atomic number to the left and below.

responding to most of the spontaneous transmutations, this is not the case for those artificially brought about.

The yield of these transmutations is very small, and the weights of elements formed by using the most intense sources of projectiles which we are able to produce at the present time are less than 10^{-15} g, representing at the most a few million atoms. It is however possible to deduce the nature of the atoms formed with sufficient confidence, by assuming, in order to write the corresponding nuclear reaction, that there is on the one hand conservation of the atomic weight and on the other conservation of atomic number between the reacting elements and those formed.

Thus the aluminium nucleus capturing a helion must be transformed into silicon when a proton is emitted

$$^{27}_{13}\mathrm{Al} + {}^{4}_{2}\mathrm{He} = {}^{30}_{14}\mathrm{Si} + {}^{1}_{1}\mathrm{H} \qquad \begin{matrix} 27 + 4 = 30 + 1 \\ 13 + 2 = 14 + 1 \end{matrix}$$

The atom formed is very probably silicon, but being present in infinitesimal quantity, it is not possible to identify it chemically. On the other hand, when the atom formed is radioactive, it can be identified by applying radiochemical methods. For example, in the case where aluminium irradiated by alpha rays emits neutrons, the rule already mentioned enables us to write the following transmutation reaction

$$^{27}_{13}\mathrm{Al} + {}^{4}_{2}\mathrm{He} = {}^{30}_{15}\mathrm{P} + {}^{1}_{0}\mathrm{n}$$

The atom formed being radioactive, it is possible to verify that it possesses the chemical properties of phosphorus.

A piece of thin aluminium sheet, irradiated beforehand by alpha rays is attacked and dissolved in a solution of hydrochloric acid (Fig. 1). The chemical reaction produces nascent hydrogen which carries over the radioactive element into a thin-walled tube where it is collected over water. This separation clearly demonstrates that some element other than aluminium has been formed on irradiation by helions. It furnishes an indisputable proof of the transmutation achieved; also, traces of phosphorus would be separated from the aluminium in the same experiment.

Finally, activated aluminium is dissolved in a mixture of acid and oxidant. To the solution is added a small quantity of sodium phosphate and a zirconium salt and it is found that the zirconium phosphate as it precipitates carries with it the radioactive element. For aluminium these experiments are

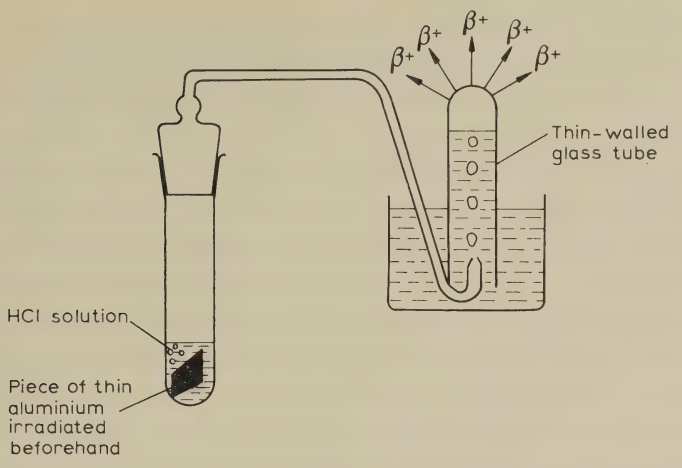

Fig. 1

delicate, for they must be made in about six minutes, the average life of the radioactive atoms which are formed being less than five minutes. Chemical tests of the same kind have shown us that the radio-element formed in boron under the action of alpha rays is an isotope of nitrogen.

We have proposed that these new radio-elements (isotopes, not found in nature, of known elements) be called radio-nitrogen, radio-phosphorus, radio-aluminium (in the case of magnesium irradiated by alpha rays) and designated by the symbols: $R^{13}N$, $R^{30}P$, $R^{28}Al$.

Immediately after these first researches, we suggested that the same phenomenon might occur for the kinds of transmutations brought about by collisions with other particles than alpha rays, for example with protons, deuterons, and neutrons.

These experiments were taken up and further developed in several countries. In England and the United States, where physicists have at their disposal equipment of very high voltages, several new elements were prepared using protons and deuterons as projectiles. In Italy first, and then in other countries, research workers, in particular Fermi and his co-workers used neutrons, projectiles which are outstandingly suitable, to cause transmutations. A large number of new elements were created in this way, among which were radio-phosphorus $R^{32}P$, and radio-hafnium, with periods of 17.5 days and several months respectively. At the present time we know how to synthesize, often by several methods (radio-aluminium $R^{28}Al$ can be made by five different kinds of transmutation) more than fifty new radio-elements, a number already greater than that of the natural radio-elements found in

the earth's crust. It was indeed a great source of satisfaction for our lamented teacher Marie Curie to have witnessed this lengthening of the list of radio-elements which she had had the glory, in company with Pierre Curie, of beginning.

The diversity of the chemical properties, diversity of the average lives of these synthetic radio-elements will without doubt enable further advances in research in biology and in physical chemistry to be made. In order to undertake this work properly, fairly large quantities will be required. This will be achieved by the use of artificially accelereated projectiles. Equipment suitable for this is already in existence in several countries. In France, we have built two installations with which we have recently been able to obtain radio-elements in quantities a hundred times greater than those which we obtained in our first experiments. This ratio will shortly be greatly exceeded.

The method of radioactive tracers until now confined to elements of large atomic weights can be extended to a large number of elements distributed over the full extent of the periodic classification. In biology, for example, the tracer method, making use of synthetic radio-elements, will simplify the problems of the location and elimination of the various elements introduced into living organisms. In this case, radioactivity serves only to determine the presence of an element in a particular region of the organism. There is no point, in research of this kind, in introducing large quantities of the radioactive tracer. The quantities are determined by the sensitivity of the radiation detecting apparatus and the size of the vegetable or animal organism. In places, which will be more readily known by the use of this method, the radiation emitted will produce its effect on the adjacent cells. For this second mode of employment, large quantities of radio-elements will be required. This will probably become a practical application in medicine.

From this overall mass of facts now evident we can realize that the few hundreds of atoms of different species which form our planet must not be considered as having been created all at one time and to last for ever. We are aware of them because they have survived. Others less stable have disappeared. It is probably some of these vanished atoms which have been recreated in our laboratories. Up to now, it has only been possible to obtain elements with a relatively brief life, extending from a fraction of a second to several months. In order to create an appreciable quantity of a much longer-lived element, an enormously intense source of projectiles would be required. Is there no hope at all of realizing this new dream?

If, turning towards the past, we cast a glance at the progress achieved by

science at an ever-increasing pace, we are entitled to think that scientists, building up or shattering elements at will, will be able to bring about transmutations of an explosive type, true chemical chain reactions.

If such transmutations do succeed in spreading in matter, the enormous liberation of usable energy can be imagined. But, unfortunately, if the contagion spreads to all the elements of our planet, the consequences of unloosing such a cataclysm can only be viewed with apprehension. Astronomers sometimes observe that a star of medium magnitude increases suddenly in size; a star invisible to the naked eye may become very brilliant and visible without any telescope—the appearance of a Nova. This sudden flaring up of the star is perhaps due to transmutations of an explosive character like those which our wandering imagination is perceiving now—a process that the investigators will no doubt attempt to realize while taking, we hope, the necessary precautions.

Biography

Jean Frédéric Joliot, born in Paris, March 19, 1900, was a graduate of the École de Physique et Chimie of the city of Paris. His father was Henri Joliot, a merchant, and his mother was Emilie Roederer. In 1925 he became, at the Radium Institute, assistant to Marie Curie, whose daughter Irène he married in 1926. He obtained his Doctor of Science degree in 1930, having prepared a thesis on the electrochemistry of radio-elements, and became lecturer in the Paris Faculty of Science in 1935. At this time he carried out considerable research on the structure of the atom, generally in collaboration with his wife, Irène Joliot-Curie. In particular they worked on the projection of nuclei, which was an essential step in the discovery of the neutron (Chadwick, 1932) and the positron (Anderson, 1932). However, their greatest discovery was artificial radioactivity (1934). By bombardment of boron, aluminium, and magnesium with alpha particles, they produced the isotope 13 of nitrogen, the isotope 30 of phosphorus and, simultaneously, the isotopes 27 of silicon and 28 of aluminium. These elements, not found naturally, decompose spontaneously, with a more or less long period, by emission of positive or negative electrons. It was for this very important discovery that these two physicists received in 1935 the Nobel Prize for Chemistry. During this time F. Joliot, who had always taken an interest in social questions, joined the Socialist Party, the S.F.I.O. (1934), then the League for the Rights of Man (1936).

In 1937 he was nominated Professor at the Collège de France. He left the Radium Institute and had built for his new laboratory of nuclear chemistry the first cyclotron in Western Europe. After the discovery of the fission of the uranium nucleus, he produced a physical proof of the phenomenon; then with Hans Halban and Lev Kowarski, joined by Francis Perrin, he worked on chain reactions and the requirements for the successful construction of an atomic pile using uranium and heavy water; five patents were taken out in 1939 and 1940. On the advance of the German forces (1940), F. Joliot managed to get the documents and materials relating to this work transported to England. During the French occupation he took an active part in the

Resistance; he was President of the National Front and formed the French Communist Party. After having been Director of the Centre National de la Recherche Scientifique (1945), he became the first High Commissioner for Atomic Energy (1946); he directed the construction of the first French atomic pile (1948). He was relieved of his duties in 1950 for political reasons. While still retaining the control of his laboratories, F. Joliot-Curie took a considerable part in politics and was elected President of the World Peace Council. On the death of Irène Joliot-Curie, in 1956, he became, while still retaining his professorship at the Collège de France, holder of the Chair of Nuclear Physics which she had held at the Sorbonne.

F. Joliot was a member of the French Academy of Sciences and of the Academy of Medicine. He was also a member of numerous foreign scientific academies and societies, and holder of an honorary doctor's degree of several universities. He was a Commander of the Legion of Honour. His recreations show him as a man of wide attainments, among which piano playing, landscape painting and reading (particularly Kipling), were predominant.

Joliot devoted the last two years of his life to the inauguration and development of a large centre for nuclear physics at Orsay. He died in Paris in 1958.

Irène Curie, born in Paris, September 12, 1897, was the daughter of Pierre and Marie Curie, and since 1926 the wife of Frédéric Joliot. After having started her studies at the Faculty of Science in Paris, she served as a nurse radiographer during the First World War. She became Doctor of Science in 1925, having prepared a thesis on the alpha rays of polonium. Either alone or in collaboration with her husband, she did important work on natural and artificial radioactivity, transmutation of elements, and nuclear physics; she shared the Nobel Prize in Chemistry for 1935 with him, in recognition of their synthesis of new radioactive elements, which work has been summarized in their joint paper *Production artificielle d'éléments radioactifs. Preuve chimique de la transmutation des éléments* (1934).

In 1938 her research on the action of neutrons on the heavy elements, was an important step in the discovery of uranium fission. Appointed lecturer in 1932, she became Professor in the Faculty of Science in Paris in 1937, and afterwards Director of the Radium Institute in 1946. Being a Commissioner for Atomic Energy for six years, Irène took part in its creation and in the construction of the first French atomic pile (1948). She was concerned in the inauguration of the large centre for nuclear physics at Orsay for which

she worked out the plans. This centre was equipped with a synchro-cyclotron of 160 MeV, and its construction was continued after her death by F. Joliot. She took a keen interest in the social and intellectual advancement of women; she was a member of the Comité National de l'Union des Femmes Françaises and of the World Peace Council. In 1936 Irène Joliot-Curie was appointed Undersecretary of State for Scientific Research. She was a member of several foreign academies and of numerous scientific societies, had honorary doctor's degrees of several universities, and was an Officer of the Legion of Honour. She died in Paris in 1956.

Jean Frédéric and Irène Joliot-Curie had one daughter, Hélène, and one son, Pierre.

Chemistry 1936

PETRUS (PETER) JOSEPHUS WILHELMUS DEBYE

«for his contributions to our knowledge of molecular structure through his investigations on dipole moments and on the diffraction of X-rays and electrons in gases»

Chemistry 1936

Presentation Speech by Professor A. Westgren, Secretary of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

Chemists have for long been expressing their conceptions of the construction of compounds of substances by stereochemical formulae which are meant to represent the reciprocal position of the atoms in molecules. For many decades collected chemical experience has been concentrated in these formulae. They have enabled us to survey the enormous diversity of chemical compounds and have given us an insight into their possibilities of reaction, as a result of which it has been possible to harvest the experience gained in practice. The structural formulae are a certain guide in all works for the manufacture of new dyes, medicinal preparations, explosives and other useful substances of the most varied nature. This year's winner of the Nobel Prize for Chemistry has stated that they reflect the chemical behaviour of the substances in such a wonderful way that even the physicist cannot doubt that they do in fact represent the essential features of the real structural principles of the atomic aggregates. These formulae do not, however, represent actual models of molecules, but only indicate the grouping of the atoms.

It is only recently that these images which the chemists have made of the structure of the molecules could be accurately checked and the orientation ascertained of the atoms in compounds of substances in their details. For this purpose chemical research has made use of the services of X-rays. When such rays penetrate into a substance in which the atoms are in any way regularly arranged, the diffracted radiation, as a result of interference, is weakened in certain directions and strengthened in others. This is the same phenomenon which causes ordinary light to be dispersed in a spectrum if the light is diffracted through a series of closely drawn equidistant lines on a glass or metal plate, i.e. through a grating. Von Laue and the two research scientists, Bragg father-and-son, showed how these interference phenomena could be utilized to determine the regular arrangement of the atoms in the crystals, and were therefore awarded the Nobel Prizes for Physics in 1914 and 1915. Debye has taken an effective share in the investigation of the phenomena which have arisen in the resultant field of research and has con-

tributed by his important initiative to the development of the X-ray crystallographic methods of investigation.

In the course of this work he soon found that even the relatively simple arrangement pattern resulting from the fact that the molecules of a gas have the same structure, can suffice to produce a detectable interference effect when X-rays penetrate a gas. As is the case with the reciprocal action of X-rays with crystals, the diffracted rays have an intensity which changes regularly with the angle of diffraction. Debye later worked out a complete theory for this phenomenon and as a result he has succeeded in creating a valuable method for the determination of the structure of molecules. A narrow sheaf of X-rays of known wavelength penetrates into a gas; the diffracted radiation is recorded, usually by photography. With the aid of Debye's theory a test is made to find whether a conceivable molecular model is in agreement with the distribution of intensity of the diffracted radiation; if such an arrangement of the atoms is confirmed, their dimensions can be ascertained and hence important information is obtained on molecular structure.

The cathode rays, which consist of high-speed negative particles of electricity – electrons – and which can therefore be called electron rays, have a wave nature, as was discovered by L. de Broglie, and so can be utilized to investigate the structure of the molecule. Consequently, Debye's theory on the interference of X-rays can readily be applied. There is, however, one difference, which is that the electron rays are diffracted mainly through the nuclei of the atoms, whereas the X-rays are scattered on the electron clouds which surround the atomic nuclei. As a result of this, the electron interferences give information on the position of the atomic nuclei in the molecule, whilst the X-ray interferences reveal where the centres of gravity of the electron clouds lie. In general, however, at least in practice, the particle systems so determined fall together. What is ascertained in both cases, then, is the position of the centres of the atoms.

The fact that matter is built up of electrically charged constituents is utilized by Debye to elaborate another very important method for investigating the structure of the molecule. According to Debye, if a substance is placed between the charged plates of a condenser, the effect of the electric field upon its molecules can be doubled. Inside every atom the positive nucleus is somewhat displaced in relation to the surrounding electron cloud, which is in consequence also deformed; furthermore the reciprocal position of the atoms in the molecule is disturbed. In addition to this deformation

effect, a direction effect must also occur in certain cases. If indeed the distribution of the charge with the molecule is asymmetrical, the field endeavours to orientate this in a certain manner. Such a molecule possesses a so-called dipole moment. With regard to the electrical effects it possesses two equally large charges, one positive and one negative, which are concentrated at a certain distance from one another. The product from this distance and the charge gives the dipole moment of the molecule. To know this size is significant, for important conclusions can be drawn from it with relation to the structure of the molecule.

Debye has elaborated a theory of the effect of electric fields on molecules and has worked out methods for the determination of their dipole moments. These can be determined by measurements of the variation of the insulating power and of the density with the temperature. Debye's theory applies strictly only for diluted gases, in which there is no need to reckon with a reciprocal effect between the molecules. It is difficult, however, to prepare the experimental material for the gases necessary for the calculation of the dipole moments. It is therefore of value that the theory, as has been established experimentally, can also be applied without noteworthy errors to diluted solutions of substances in non-polar solvents.

A large quantity of important information has been collected on the structure of both inorganic and organic molecules by investigations according to these new methods, which complement each other in an outstanding manner. At least one hundred gaseous substances have already been studied now with the help of X-ray and electron interferences, whilst the molecular structure of thousands of substances has been elucidated by dipole moment measurements. Investigations of the charge symmetry of molecules have been of very great value especially to organic chemistry. It has been shown that certain bonds between atoms in organic compounds are characterized by specific electric moments. But characteristic moments can also be ascribed to groups of atoms or radicals. These bond or radical moments can in general be concentrated with a sufficient degree of accuracy to a resultant total moment, somewhat like the forces acting upon a body can be replaced by a resultant. A structural formula can therefore be checked by calculating its dipole moment and by comparing the result obtained with the dipole moment found by experiment.

The measurements of the dipole moments, as well as those of the X-ray and electron-ray interferences in gases, are being utilized more and more, together with other investigations on molecular structure, as an essential aid

to constitutional determination. The form of the molecules, the distance between their atoms, and also the greater or lesser degree of movement of certain groups entering into the molecules can now be exactly measured. This is obviously important in such cases where we have to deal with chemical compounds of identical composition but of different structure, i.e. where isomerism is present. During the last decade no means of research has been made available to organic chemistry which has been, even approximately, so effective in its importance.

The Royal Academy of Sciences attaches such a high value to the work which has led to these results that it has found it deserving of the award of this year's Nobel Prize for Chemistry.

Professor Debye. Your rich scientific activity has been aimed in particular to research into the structure of matter. Your wealth of ideas, your penetration and your secure mastery of mathematical methods have yielded great success to your endeavours, and your results have enriched chemistry to an extraordinary degree in all kinds of ways. By your investigations on dipole moments and also on X-ray and electron interferences in gases you have widened and deepened our knowledge of molecular structure to such an extent that the Royal Academy of Sciences has awarded you the Nobel Prize for Chemistry. In extending to you the sincere congratulations of the Academy I ask you to accept the prize from the hands of His Majesty the King.

Peter Debye

Methods to determine the electrical and geometrical structure of molecules

Nobel Lecture, December 12, 1936

Long before we had at our disposal the means offered to us today by the quantum theory to discuss the structure of atoms and molecules, it was clear that in debating this subject we had to deal with electrical structures. Starting from this point of view it seemed appropriate to me in 1912, therefore, to establish what conclusions could be reached with regard to the distribution of electricity in the molecule on the basis of experience with the action of the simplest conceivable electrical disturbance by means of a static field[1]. Since Faraday had introduced the measurement of this disturbance by the aid of the dielectric constant it was usual to consider the reason for the polarization occurring in every insulator on which the dielectric effect is based to be the displacement of the charges produced in the molecule by the field and which disappears again as the field disappears. This concept is still valid today. We know, indeed, that the deformation of the charge structure, which occurs with the normal experiments, is extremely small. For instance, in the helium atom, the displacement of the electron cloud against the nucleus in a field of 300 volts/cm only amounts to about 2.10^{-16} cm, i.e. a small fraction of the nucleus diameter. Owing to the size of the elementary charge, this tiny displacement is, nevertheless, still large enough to produce easily observable dielectric effects. If, however, a list of the dielectric constants of various bodies is considered, preferably based on measurements for the gaseous state, because there are no complications to be feared here owing to reciprocal influence of the molecules, abnormally large susceptibilities will be found for many molecules, and a particularly great mobility of the charges cannot be regarded as the cause of these. Thus, for example, the molecules of NH_3 and H_2O show a susceptibility which is some 40 times greater than that of the Ne atom, although the three mentioned particles contain the same number of electrons. The fact that a powerful loosening of the electron bond representing the hydrogen valency is not happening will be seen if the susceptibility of the molecules of H_2 and CH_4 is used as a comparison, as they both show only a normal small value. By working on observations

of this nature we can come to the conclusion that often besides the deformation there must also exist another cause of the observed electrical polarization. Now even before 1912 paramagnetic polarization and its diminution, observed by Curie, with an increase in temperature were explained in the theory of Langevin[2] by orientation of permanent elementary magnets. I therefore conjectured that molecules in the state of equilibrium can also be carriers of a permanent electric moment and so the electric polarization in general must be attributed to two simultaneously effective causes, a deformation and an orientation. Molecules with abnormally great electric susceptibility are, then, those with a relatively large permanent moment and its orientation causes the large polarization. This same hypothesis was published a few years later by J. J. Thomson[3].

As both effects are added in the dielectric constant measured, a method had now to be found of observing them separately. A first process for this purpose results in the transference of Langevin's calculation to the electrical case. The orientation obtainable in a field is the result of an equilibrium between the field effect, which is striving for an orderly arrangement of the dipole directions, and the effect of the heat movement, which is creating disorder. With increasing temperature the mean moment arising from the orientation and produced through a uniform field must therefore decrease, and this is also the result of the theory which for this mean moment gives the value $\mu^2/3kT$, where μ is the permanent moment in electrostatic units, k is Boltzmann's constant and T is the absolute temperature. The assumption here is that the potential energy of a dipole in the field is small against the mean thermal energy of a molecule, otherwise proportionality between the field strength and the polarization produced does not exist. This condition is in fact fulfilled in the great majority of the measurements. From the size of the elementary charge and the dimensions of the molecules it can be deduced that μ should have values of the order 10^{-18} (in electrostatic units), and this means that in a field of 300 volts/cm the thermal energy at room temperature is still always about 40,000 times as large as the above-mentioned potential energy. Originally the theory was purely classical. Since the appearance of the quantum theory doubts have arisen regarding the numerical factor of $\frac{1}{3}$ in the formula for the mean moment; actually other numerical factors were calculated. Since, in the meantime, the methods of calculation of the quantum theory have been definitely formulated in wave mechanics, the factor $\frac{1}{3}$ has been re-established as correct[4]. A further question which still required an answer was whether the moment produced by the

deformation was not also susceptible to temperature. In agreement with the conceptions which were prevalent 25 years ago, it was at that time shown that the quasi-elastically bound electrons through their displacement produce a moment which is independent of the temperature. Today we would prefer to attribute the actual insusceptibility of displacement against increase of temperature to the fact that the difference in energy between the basic distribution of the electrons and that under excited conditions is in general so great that the latter do not occur in any noticeable frequency.

Expectations have been confirmed by experiments on the dependency of the dielectric constant of different gases upon the temperature, conducted by Bädeker[5] even before the theory appeared, and by Jona[6] at my suggestion after its appearance, and then, when electron tubes were available by beautiful and exact measurements by Sänger[7] and C. T. Zahn[8], *inter alia*. The observable mean moment of a molecule produced through an electric field is in fact a linear function of $1/T$; the experimentally determined factor of $1/T$ in this presentation yields numerical values of the dipole moment of the order of 10^{-18}. We shall later come back to the connection of the measured moments with the molecular structure. At this point let us make just one remark on the relative significance of deformation and orientation. Very often the latter is the decisive one; a good example is given by the NH_3 measurements from which it is seen that at room temperature 90% of the susceptibility are due to the orientation of the permanent dipole and only 10% to the deformation.

We come to a second method of determining the dipole moment if the question is considered of the dispersion of the dielectric constant. If we now first confine ourselves to considering the gaseous state again, there exist relatively sharply defined quantum stages of rotation, between which transitions will take place under the influence of the incident radiation. This means that a series of absorption lines exists, of which the first will lie for molecules with larger moments of inertia at a wavelength of the order of 1 cm. If we now pass through the infrared in the direction of increasing frequency, the refractive index in the neighbourhood of each absorption line will show the well-known breaks, and for the determination of its size the influence of the rotation and of the permanent moment will more and more disappear. The orientation can no longer be established, therefore, with high frequencies, and the frequencies of visible light must be considered as such. Only the influence of the deformation is left, for in general the electrons only cause absorption in the ultraviolet part of the spectrum. According to Maxwell's

relation therefore, the square of the optical refractive index (possibly after extrapolation to infinitely long waves, without taking into consideration the above-mentioned ultrared absorption lines) may be regarded as that part of the dielectric constant which is only based on deformation. In this way a separation of the two effects is again achieved and a determination of the dipole moment obtained. The method is clearly very simple, for it requires only the formation of the difference of the dielectric constant and the square of the optical refractive index. It is in fact always usable with good success if the molecule is sufficiently strongly polar. With low polarity the errors of estimation of the static deformation fraction become too important[9].

A third interesting method is offered by the observation of the deflection of a molecular ray in an inhomogeneous electric field. As a result of the deformation alone there is a deflection of the ray only in the direction of an increasing square value of the deflecting field strength. The existence of a permanent dipole moment, creates a widening of the ray. Experiments of this nature were conducted by Wrede[10], by Estermann[11] and, recently, by Scheffers[12]. Exact determinations of the dipole moment are so difficult to obtain because its size has to be concluded from the widening of the ray. The method is, however, very valuable for special cases which would otherwise not be accessible by the usual methods. It did good service in the elucidation of the peculiar behaviour of pentaerythritol and substitution products[11] and also in the determination of the large moments of alkali-halogenide molecules ($\mu = 6.3 \cdot 10^{-18}$ for KCl)[12].

In discussing the methods so far mentioned I have restricted myself exclusively to measurements on gases, because only thus is it possible in a completely unobjectionable way to denote the field strength actually acting upon the molecule, and because only in gases of low density can the orientation of the molecules be regarded as entirely free. On the other hand, the material accessible in such experiments is very essentially limited. For this reason I decided in 1916 to ignore the objections and to determine moments by measurements on diluted solutions of polar substances in non-polar solvents[9]. It is now first of all necessary to estimate the influence of the neighbouring molecules. This was done by applying the relation of Clausius and Mosotti. It is then shown that the susceptibility of the molecule now no longer follows immediately from the excess of the dielectric constant above 1. Now $4\pi/3$ times the moment produced in the n molecules of the unit of volume under the effect of the unit field strength is measured by the fraction $(\varepsilon - 1)/(\varepsilon + 2)$. The excellent constancy established experimentally of the

molecular refraction calculated according to the Lorentz-Lorenz formula in the transition from the gaseous to the liquid state guarantees that, at least for non-polar molecules, the Clausius-Mosotti method of calculation may also still be applied for the frequency 0. Nevertheless it is always essential throughout the experiment to see that the reciprocal influence of the polar molecules is infinitesimally small. This will be achieved if, to determine the moment, only sufficiently diluted solutions are used, or by extrapolation to infinite dilution of the measured values, limiting values are obtained for the dielectric effect of the dissolved molecules. A second condition is that the polar molecule should not be influenced either in its moment or in the freedom of its adjustment by the surrounding non-polar molecules of the solvent.

The method consists, then, in the determination, by measurements of the dielectric constant of diluted solutions, of the mean moment of the polar molecule in a unit field, and next in the separation, by measuring the refraction, of the orientation fraction from the deformation fraction. As a variant it was later proposed by Errera[13] to infer the last-named fraction from measurements on solids.

After the first measurements of this kind had been made at my suggestion by Miss Lange (Göttingen thesis, 1911)[14] and later measurements had been very much simplified by the introduction of electron tubes and the beat-method, in the course of time a very large number of molecules had been investigated regarding their polarity by many observers, amongst whom I would like to mention in particular Ch. P. Smyth[15] and J. W. Williams[16]. In an article in the *Handbuch und Jahrbuch der Chemischen Physik* for 1935, O. Fuchs and K. L. Wolf[17] published a list of the dipole moments of 1,100 substances; 12% of these proved to be non-polar. A very valuable summary of dipole moments has also been published by the Faraday Society, edited by Sidgwick[18].

We can also consider investigating the diluted solutions at different temperatures and then, as with gases, from conclusions on their polarity from the temperature coefficients of the susceptibility of the dissolved molecules. This is indeed the most exact method of moment determination when applied to gases. In the case of solutions, however, solvent influences appear which are not taken care of in the simple theory and although they do not make the method unusable, its accuracy is affected and it cannot be given preference over the dispersion method. As the latter is also far simpler to operate, the temperature method has only occasionally been used for solutions.

With this remark we now touch upon a section of the development to which increased attention has been paid of late. As an assumption for the completely faultless functioning of the dispersion method, a second condition was mentioned above as required, viz. that there should be no influences of any kind of the solvent upon the dissolved molecules. The validity of this assumption was of course tested at the outset of the development of the method by J. W. Williams, *inter alia* [19]. The question was whether for a definite molecule the same moment was found in different solvents. At that time the validity of this assumption was found within the experimental limits of error. When, more recently, H. Müller[20] at my suggestion carried out more exact measurements with improved experimental methods, it was shown that there does exist an unmistakable though small influence of the solvent, which means that for the same molecule in different solvents not exactly the same moment is found. The results of the experiments were also confirmed from another source, and different authors tried to substantiate and to evaluate theoretically the influence of the solvent. I do not have the impression that in this point we succeeded in obtaining full clarity, and I therefore tried last year to obtain an insight into the dielectric behaviour of pure and undiluted polar fluids, in which the reciprocal influence of the molecules is particularly strong, and in which we are compelled to expect large effects. It is in fact impossible to predict the dielectric behaviour of liquids, such as water, alcohols, nitrobenzene, etc. on the basis of the theory valid for gases. The molecules behave in these cases throughout as if their moment is smaller than that observed for free particles. Exactly similar conditions are present with the Kerr effect. Here too, experiment showed that even non-polar molecules, when near each other in the liquid, behave as if the differences of their polarizability are smaller in different directions (upon which the Kerr effect is based) in the liquid than in the gas. Obviously we can think just as little in this case of a real change of the electron structure of the molecule as of a real change of moment in the case of the polar molecules, for the refraction which depends on the sum of the polarizabilities in the three main directions is scarcely influenced by the liquefaction. Now from the clear interferences, which monatomic liquids themselves produce, when they scatter X-ray light, and also from the fact that monochromatic visible light is split by ordinary Rayleigh scattering into a narrow triplet, we must conclude that there is already present in the liquid state a quasi-crystalline structure of the molecular arrangement which limits the molecular movement. From this it follows that just as little as the translatory motion, can the rotation of the

molecules in the liquid be considered as free. In fact, as I have tried to show, we can understand the dielectric behaviour of polar liquids if we pay attention to the limitation of the free rotation and use the well-known dielectric constants in co-operation with the measured moments in the gaseous state to estimate the potential energy which hinders free molecular rotation. Values were found[21] for this energy which can amount to a multiple of the thermal energy kT.

These considerations are also of particular importance for an other effect which is characteristic in general for the existence of an orientation of the molecules. Small field strengths produce a polarization through orientation which is proportional to the field strength. But if a very strong constant field is applied and then a measurement is taken of the additional polarization produced by a superimposed weak field, then according to the dipole theory we must now expect that a lower polarization effect will take place, for the molecules are in part already adjusted by the strong field. Herweg[22] was the first person able to show experimentally that in fact this so-called saturation effect does exist and that its order of magnitude for ethyl ether is as expected. It was found, however, in experiments by Malsch[23] on strongly associating liquids such as water, the alcohols, etc., that the effect was very much smaller than is to be expected from the theory of freely rotating dipoles. In this case the consideration of the quasi-crystalline structure of the liquids again gives the explanation. The partly extremely large differences observed follow quantitatively on the basis of the same values for the energy involved in the hindering of rotation as they must be introduced to explain the values observed for the dielectric constants of the liquids[24].

Simultaneously with the development of the dispersion method in its application to liquids, the important question comes to the fore: how then in this case does the disappearance of the orientation take place in detail with increasing frequency? There cannot be any occurrence of sharp energy stages of a free rotation in a liquid, as there is with a gas. The idea of the polar molecule being compared to a fairly large particle, to which frictional resistances are opposed in its rotation, would correspond more to reality. But if this is the case, then it will be characteristic for the polar liquids that an orientation produced by an outer field does not adapt itself immediately to the new conditions when the field suddenly disappears, but needs some time to go over again to complete disorder. Or, in other words: there does exist a time of relaxation, and its magnitude is determined by the dimensions of the polar molecule and by the viscosity of the liquid. On this basis a

theory can be built up of orientation under the influence of any time-dependent fields. In its application to periodically changeable fields this leads on the one hand to the result that the degree of orientation will be less at higher frequencies, that is to say: an anomalous dispersion of the dielectric constant must exist for all polar liquids. The range of frequency which is decisive for the decrease of the dielectric constant, in the case of ordinary liquids of not too high a viscosity, should correspond to electric waves of a few centimetres of wavelength. On the other hand, owing to the phase difference between field strength and polarization, the anomalous dispersion should be connected with the appearance of dielectric losses[25].

It was exactly these phenomena which were discovered by Drude in a series of non-conducting liquids, and there can be no doubt that they are indeed caused by the polar structure of the molecules. The marked temperature sensitivity of the anomalous dispersion and absorption corresponds to the large temperature coefficients of the macroscopically measured viscosity, as was proved particularly clearly by experiments conducted by Mizushima[26]. This means that the transference of the usual viscosity laws to particles of molecular dimensions is not devoid of all justification. We can make more exact quantitative predictions in particular for relatively large molecules. This is an interesting connection, for in this way, by observation of the dielectric dispersion and of the losses with high frequency, we obtain a means of determining the dimensions of large molecules. Recently experiments are being made to determine the relaxation time from the dielectric losses of diluted solutions of polar substances in non-polar solvents, and to bring it into relationship with the molecular constants. I have the impression that in these experiments as in the case of the losses shown by pure polar liquids, the theoretical approach to the actual conditions can be improved by the consideration of the quasi-crystalline structure of the liquids[21,25]. This thought is so much more obvious since conversely dispersion and absorption are observed in fixed bodies, as was first discovered by Errera[27] for ice. In this and in similar cases, as stressed by Pauling[28] in particular, we have to do with crystals in which atom groups can more or less freely rotate, and which are consequently internally partly « liquid ».

After having tried in the preceding part to give a survey of the methods of determining the dipole moments and their part in the elucidation of the dielectric phenomena, we must now discuss their significance for problems of the actual molecular structure. In view of the extension which this branch has assumed it is impossible to offer a comprehensive presentation. I must

be satisfied with pointing out the guiding principles by means of some characteristic examples[17, 18].

The atoms of the inert gases are non-polar, corresponding to the centrally symmetrically structure of their electron clouds. In the same way diatomic molecules consisting of two equal atoms (N_2,O_2) have been proved to be non-polar. On the other hand, polarity immediately appears as soon as the two atoms are different. This polarity is small if both atoms are close to each other in the periodic table (CO) and it only becomes large in the case of molecules like HCl. The magnitude of the moment, however, does not in any way correspond to the value which would be proper to a structure which would consist of a H-ion and a Cl-ion at their actual nuclear distance. The actual moment, $\mu = 1.04 \cdot 10^{-18}$, is only about $\frac{1}{6}$ of that value. If we consider a HCl molecule as having been created by two ions brought into close proximity, there is then a considerable penetration of the H-nucleus into the electron cloud of the Cl-ion, by which $\frac{5}{6}$ of the originally existing moment is compensated. An actual quantum-theoretical calculation of the moments does not appear to be easy. In any case, up to now the calculation of Kirkwood[29] for the molecules HF, HCl, HBr and HI is the only one which has led to a result.

Molecules which consist of three atoms can be divided into two groups: CO_2 and CS_2 are non-polar, but the molecules H_2O, H_2S and SO_2 have a permanent moment. The explanation is that in the first case the arrangement of the atoms in the molecule is linear, whereas in the second case the atoms are situated at the corners of a triangle. The moments of inertia, resulting from the analysis of the band spectra, provide an independent proof of those structures. Similarly, the observed polarity of the molecules NH_3, PH_3 and AsH_3 leads to a structure in which N, P, or As are placed at the apex of a three-sided pyramid and the three H atoms at the corners of its base.

From the measurements by Sänger[7] on the series CH_4, CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4, it follows that the first and also the end members of this series are non-polar, but the intermediate members are all polar. This fits in beautifully with the views introduced into organic chemistry by Van 't Hoff on the carbon valencies.

In the case of the ethylenes doubly substituted with Cl or Br, the *cis*-form has a considerable moment, as shown by Errera[30], whilst the symmetrical *trans*-form is non-polar, again in agreement with the structural formula. The measurement of the polarity, generally speaking, in many cases of *cis-trans*-isomerism forms an excellent and easy means of determining the two forms.

For the rest, it should be stressed that neither the double bond nor the triple bond between two C atoms has in itself any polarity. Both ethylene and acetylene are non-polar.

In the same way all saturated hydrocarbons are non-polar, whether with branched or non-branched chains. We shall certainly have to award a moment to the CH bond as such, but nevertheless all the molecules are non-polar, as Smyth stresses[15], if we adhere to the tetrahedral valency orientations, because then every CH_3 group is precisely able to compensate a CH bond electrically.

Thus we have made a start with a division of the entire moment into individual moments of the bonds, which are combined by means of vectorial addition to a resultant moment, like forces. (Absolute values for the individual bonds were given in detail for the first time by Eucken[31]). This construction, stipulated by the nature of the electric moment, has proved reliable throughout all the discussion of the molecular structure based on moment measurements. It is true that this description is only an approximation in so far that on more intimate inspection due consideration must be given not only to an additional influence of the adjacent valency orientations, but also to the electrical influence of the molecular structure arising from the moments. This does not, however, prevent the simple method from being a highly valuable means of achieving a first and good approximation.

The first instance which I know of as arising from this point of view, and which was indeed discussed by J. J. Thomson[32], was that of the disubstitution products of benzene. If, for example, the moment of monochlorobenzene is known, we should be able to calculate the moments of ortho-, meta- and paradichlorobenzene by combining to a resultant two equal monochlorine moments vectorially with angles of 60°, 120°, and 180°, based upon the structure of benzene characterized by the regular hexagon of the C atoms. It is correct that the para-substitution product is in fact non-polar; on the other hand, the calculated numerical values of the two other products, and particularly those of the ortho-substituted benzene, are not quite in agreement with the experimental findings. Obviously we have to deal in this instance with a reciprocal influence of closely adjacent groups, which leads to a spreading-out of the valence directions.

If two different atoms or groups are substituted in para-position, the resultant moment can be both equal to the sum and equal to the difference of the individual moments. One would expect this, for whether the sum or the difference occurs, will depend on whether, in the substituted groups,

like or unlike charges show externally. A means is thus obtained of distinguishing positive and negative groups (in the purely electrostatic definition) one from another.

Finally, it can even happen in the substitution of two equal groups in para-position that a polar molecule does occur, nevertheless. For instance, the moment of hydroquinone-dimethylether, in which two O-CH_3 groups are substituted in para-position at the benzene ring, is $1.73 \cdot 10^{-18}$. Such and similar results are explainable by the fact that the moment of the individual groups does not lie in the plane of the benzene ring. It is clear that the two valence directions of the O atom form a smaller angle than 180°, as is the case with the H_2O molecule. This, together with the more or less free rotatability of each group around the axis, which is present from the C atom of the benzene nucleus to the O atom, means that apart from entirely special positions of the two O–CH_3 directions the molecule will always have a resultant moment, and therefore in the experiment a mean moment must be observed. It is clear that by combinations of measurements on suitable substitution products we can draw valuable conclusions both regarding the valency angle and the greater or lesser freedom of the rotation, and in fact in many cases polarization measurements have been used for this purpose.

A particularly interesting case occurs when the potential energy which restricts the freedom of rotation is comparable with the thermal energy of the surrounding temperature. Such a case is, *inter alia*, 1-2-dichloroethane, in which a rotation of the two CH_2Cl groups can take place round the C–C bond. The position with the least potential energy in this instance is the *trans*-position, to which as such the moment zero is proper. With increasing temperature the amplitudes of distortion become increasingly greater and finally, with a sufficiently high temperature, all the distortion angles are equally justified. A moment is however associated with this situation and hence we must expect that the «permanent» moment of the molecule observed at different temperatures will not be constant, but will increase with increasing temperature to a limiting value. In fact that is the result of the observation; the temperature curve can be utilized to deduce quantitative statements regarding the amount of work required for the rotation of the groups[33].

The conviction of chemists that the structural formula is in fact a representation of the spatial arrangement of the atoms in the molecule which corresponds to nature is obviously brilliantly confirmed by the previous discussion. Often the only thing lacking is that the representation is not ac-

cording to scale. A method should therefore be sought to carry out measurements of the distances within the molecule. Since the discovery by von Laue[34] of crystal interferences we know that the wavelengths of X-rays are small enough to be suitable for this purpose. If, however, we wish to examine free molecules, the difficulty arises that we have to operate with particles which cannot be fixed in a definite orientation in space, like a crystal. Fortunately, however, I was able to show[35] that every atomic structure irradiated with X-rays must produce recognizable interferences in its scattered radiation, even when it changes its orientation in space continuously and uncontrollably. I was led by this consideration, when together with Scherrer[36], the interferences of crystalline powders and of liquids were discovered. These experiments were a preliminary step to the first attempt to produce interferences by scattering on CCl_4 vapour, carried out in 1928 together with Bewilogua and Ehrhardt[37,42].

The basis for the interpretation and evaluation of such scattering curves is based on the following calculation. The intensity of the scattered X-ray light decreases gradually with increasing angle ϑ between the primary and secondary ray as well for atomic as for molecular gases and it does so as a result of an interference effect. In the case of the atoms, this decrease follows a smooth curve, but in the case of molecules, on the other hand, actual maxima and minima occur in the scattering curve occasionally reduced to undulations only. Such a scattering curve can be constructed by superposition of as many individual curves as there are atomic distances in the molecule. If the molecule consists, for instance, of N atoms, for which an enumeration $1 \ldots m$ or $n \ldots N$ is assumed, then for the intensity the following expression is obtained, neglecting a factor, which here is unessential:

$$I = \sum_{m=1}^{N} \sum_{n=1}^{N} \psi_m \psi_n \cdot \frac{\sin x_{mn}}{x_{mn}}$$

The magnitude x_{mn} is here proportional to the distance l_{mn} from atom m to atom n and, if the primary wavelength λ is used for irradiation, it is defined by the relation:

$$x_{mn} = 4\pi \frac{l_{mn}}{\lambda} \cdot \sin \frac{\vartheta}{2}$$

The magnitudes ψ_m or ψ_n are the so-called atomic form factors of the atoms m or n respectively, and represent the amplitudes dispersed by those atoms.

Every atomic distance in the molecule therefore produces for itself an intensity which increases and decreases with the increasing angle ϑ, in accordance with the function $\sin x/x$. For large atomic distances, the maxima lie close together, they get farther apart for small distances. The relative importance of the different atomic distances is measured by the product of the atomic factors ψ. These can be calculated by various methods (Thomas-Fermi, Pauling-Sherman[38]) or they can be taken with greater accuracy from the tables drawn up by Hartree[39]. For small angles such an atomic form factor is simply proportional to the number of electrons contained in the atom. Consequently, for the distribution of intensity, the distances between the atoms of fairly large atomic weight have the most importance; the distances between the light and heavy atoms are of less importance and the least important are the distances between light atoms.

We must also take into consideration that with scattering, polarization of the radiation occurs, and so the intensity in the neighbourhood of the 90° direction is reduced. Furthermore, each diagram has a background of incoherent radiation which in accordance with the Compton effect has changed its wavelength and does not contribute to the interferences. No allowance was made in the formula for these circumstances, which are to be considered more as corrections.

The fact that the first experiment was conducted on CCl_4 gas was not an accident. If we take the tetrahedron as the basis for the structure of this molecule there occur in it four equal distances between the heavy Cl atoms beside four distances which are equal between the light C and the heavy Cl atoms, though according to what we stated above, these latter distances are much less important. It could therefore be hoped that there would be a distribution of intensity which would show relatively pronounced maxima and minima of intensity, and the experiment confirmed this expectation. To determine the atomic distances in the molecule, we need only compare the observed angular position of the maxima and the minima with that resulting from the theoretical representation. With a known wavelength of the primary radiation, a proper choice of the atomic distances has to be made in order to obtain agreement between theory and experiment. This is particularly simple in the case of CCl_4, as the tetrahedron is completely determined by a single length, the length of edge for instance. In making an exact comparison we must of course require that not only attention is paid to the position of the maxima and minima, but that the intensity curve throughout its entire length coincides with the theoretically calculated curve. Careful

experiments in this direction, using purely monochromatic primary radiation obtained by crystal reflection, were carried out by Van der Grinten in the Leipzig laboratory[40]. The excellent agreement shown in this instance can be regarded as direct experimental proof of the regular tetrahedral structure of the CCl_4 molecule.

After the scattering experiments with X-rays[37, 42] had shown that interferences can be obtained from the individual molecule, Mark and Wierl published in 1930[41] the first results of similar experiments with cathode rays. Since, according to de Broglie, electron rays can interfere with one another with the wavelength $\lambda = h/p$ (h = Planck's quantum constant, p = electron impulse), this method was also successful. If both methods are compared, the advantage of the cathode-ray method lies in the fact that, because of the much stronger interaction of the electrons with the electric charges in the atom, the exposure times here are much smaller (of the order of one second), whereas in the case of X-rays they amount to hours. Secondly, with the usual voltages the wavelength of the cathode rays (0.07 Å with 30,000 volts) is essentially smaller than that of the X-rays utilized (about 1 Å). As a result, the interferences can be taken and followed up to higher orders. On the other hand, the X-rays have the advantage that recordings for complete intensity curves can be obtained without much difficulty. In addition, there is the fact that the background arising from the incoherent radiation increases with increasing angle starting from zero at zero angle in the case of X-rays, whereas in the electron-case the largest intensity occurs for small angles. Consequently, with X-rays the maxima are more strongly pronounced.

The question now arises, with what accuracy the distances in the molecule can be determined from the maxima which are only indistinct in any case because of the low number of the interfering atoms. We can establish this very well on the basis of experiments of both kinds on the CCl_4 molecule, which has gradually become a kind of standard substance. Bewilogua[42] finds 2.99 Å for the Cl–Cl distance in 1931 with X rays, and Wierl[43] 2.98 Å shortly afterwards with cathode rays. The next two years, 1932 and 1933, bring three further publications with cathode rays, which lead to the values 2.98, 2.97, and 2.98. Work with cathode rays is continued in more places; in 1933 one publication gives the smaller value 2.91, and then in 1934 there are four further results with cathode rays which yielded the still smaller values 2.87, 2.86, 2.85, and 2.87[47,48,49,50]. This induced me, when I was Francqui Professor at Liége to build an X-ray and a cathode-ray apparatus in order to check the problem of the exact value of the distance again.

Degard and Van der Grinten[44,45] find 2.86Å in 1935 with cathode rays, and Piérard and Van der Grinten[44,46] obtain 2.85Å with X-rays. It is therefore quite certain that the value found at the start of the development was about 4% too high, and that the value 2.86 Å, with a tolerance of ±0.01 Å, is to be regarded as the correct one. The above-mentioned measurements from 1934 by Brockway and Pauling[47], Cosslett and de Laszlo[48], by Cosslett[49] and by Brockway and Wall[50] are also in agreement with this.

In the seven years which have elapsed since 1929 many other molecules besides CCl_4 have been investigated interferometrically; in a handbook article by Hengstenberg and Wolf[51] in 1935, a list of 66 substances has been given, and in an article by Brockway in the *Review of Modern Physics*[52] in 1936, there is a list of 143 substances. Exact distance details, as contained in such tables, are of special interest, because they allow interesting conclusions on the nature of the bond as emphasized for instance by Pauling. Moreover, the picture we receive of the spatial structure is of importance. Here we have only space for a few incomplete details which should be enough to create a general impression.

Bewilogua, in publication of 1931[42], had already shown for the series CCl_4, $CHCl_3$, CH_2Cl_2, and CH_3Cl how with decreasing Cl-content the diagram changes as expected from the tetrahedral structure. At the same time the conclusion was drawn that an increase of the Cl–Cl distances goes together with a reduction of the number of Cl substitutions. The latter result has been doubted at times, but newer measurements with both methods show unanimously[53,54] that, to begin with, in the case of chloroform the Cl–Cl distance is in fact 3.5% greater than in CCl_3, i.e. by the same relative amount which Bewilogua deduced. There is therefore a repulsion between the Cl atoms, as one would expect from the observed dipole moments.

Wierl[43] has shown, and other observers have confirmed, that besides CCl_4 the analogous molecules $SiCl_4$, $TiCl_4$, $GeCl_4$, and $SnCl_4$ possess the tetrahedral structure. It is interesting that the same applies for $Ni(CO)_4$, as recently found by Brockway and Cross[55]. The molecules CO_2 and CS_2 are shown by interferometric measurements to be linear, in agreement with the fact that their dipole moment is zero. It has also been possible to prove that in the molecules SF_6, SeF_6, and TeF_6, the fluorine atoms occupy the corners of a regular octahedron[51,52].

That the interferometric methods are able to distinguish between *cis-trans*-isomers has been shown for the dichloroethylenes. The *trans*-form has substantially larger Cl–Cl distance than the *cis*-form, which is what it ought to

have. If there is a single bond between the two C atoms, instead of a double bond, the question again comes to the fore, as in the case of the dipoles, of the freedom of rotation around the C–C bond. It is of particular interest that it is also possible to prove interferometrically the preference of the *trans*-position, as was likewise inferred from the temperature dependence of the dipole moment[56].

For the benzene molecule, and particularly beautifully for hexachlorobenzene, it can be proved that the six-membered ring is planar and that it corresponds to the carbon ring of graphite and not to that in the diamond[57]. This is also indicated by the C–C distance itself, which has a value of 1.54 Å in aliphatic compounds, but only 1.41 Å in aromatic compounds. It becomes still smaller with double or even triple bonds[51,52].

Finally, two general questions may be raised which so far have not been answered in full.

Is it possible by using interferometric methods to measure the thermal oscillations of the atoms in the molecule? Experiments and measurements by James[58] led to the result that in the molecule $SiCl_4$, which was selected because the Cl atoms are somewhat more loosely bound than in CCl_4, the oscillations are too small to allow certain proof with the aid of X-ray interferences. From Raman-effect measurements the conclusion can be drawn that in most molecules the elastic constants are in fact relatively large; for instance, the C–C bond in aliphatic hydrocarbons is as hard as it is in the diamond. Recently Van der Grinten[44] has explained the flattening of the intensity curve for CCl_4 in the vicinity of the 5th maximum (obtained with electrons) as due to the influence of atomic oscillations. So it seems possible that by the investigation of the intensity curve of electron recordings in the neighbourhood of suitably selected interference maxima of high order, the atomic oscillations can be traced.

Can we determine by interferometric methods the position of the hydrogen atoms? It will hardly be possible to do so with X-rays, for as the X-ray scattering is due to the electrons, it is necessary for these to be present in a satisfactory concentration in concentric distribution around the nucleus whose position is to be measured. This is, however, not the case with the H-nucleus. On the contrary, as recent experiments by Thomer[59] show, the molecules Ne, H_2O, NH_3, and CH_4 with the same total nuclear charge all scatter almost like monatomic gases. The only thing clearly indicated is, that the electron cloud is the more extended, the more the total nuclear charge of 10 unit charges is distributed on individual nuclei. It has not yet been

decided experimentally whether the electron scattering, which with larger angles chiefly takes place at the nucleus, can be better utilized here. Provisionally it is in any case more practical to replace such hydrogen atoms (the position of which is of particular interest) chemically by heavier atoms, such as Cl.

In summary I would like to emphasize that the physical methods discussed here besides furnishing a precise definition of atomic positions have given a brilliant confirmation of structures obtained by purely chemical means.

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Biography

Petrus (Peter) Josephus Wilhelmus Debye was born March 24, 1884, at Maastricht, the Netherlands. He received his early education at the elementary and secondary schools in his home town and from then on his life has been devoted to a search for knowledge. He continued his studies at the Aachen Institute of Technology (Technische Hochschule) and gained a degree in electrical technology there, in 1905. This led to his appointment as Assistant in Technical Mechanics at the Aachen Technological Institute, where he worked for two years. In 1906 Debye obtained a similar position in Theoretical Physics at Munich University, where he qualified as a University lecturer in 1910 (having obtained this University's Ph.D. in Physics in 1908).

In the following year, i.e. 1911, Debye became Professor of Theoretical Physics at Zurich University, where he remained for two years. He returned to The Netherlands in 1912, when he was appointed Professor of Theoretical Physics at Utrecht University, and in 1914 he moved to the University of Göttingen, to take charge of the Theoretical Department of the Physical Institute. Later, he became Director of the entire Institute and lectured on experimental physics until 1920.

In 1915 Professor Debye became Editor of *Physikalische Zeitschrift* and continued to act in this capacity until 1940.

Debye returned to Zurich in 1920, as Professor of Physics, and Principal of the Eidgenössische Technische Hochschule. In 1927 he held the same post at Leipzig and from 1934 to 1939 he was Director of the Max Planck Institute of the Kaiser Wilhelm Institute for Physics in Berlin-Dahlem and Professor of Physics at the University of Berlin.

This appointment terminated his work in Europe, and in 1940 he became Professor of Chemistry and Principal of the Chemistry Department of Cornell University, Ithaca, New York, taking American citizenship in 1946.

The year 1952 saw Debye's resignation of his post of Head of the Chemistry Department at Cornell University and his appointment later as Emeritus Professor of Chemistry at Cornell University.

Professor Debye was wedded to Physics and Chemistry and his devotion

to his work gained him many distinctions, and Honorary Doctorates have been conferred upon him by the following universities and learned institutes: Brussels and Liège; Oxford; Sofia; Mainz; Technische Hochschule, Aachen; Eidgenösissche Technische Hochschule, Switzerland; and in the United States: Harvard; St. Lawrence; Colgate; Nôtre Dame; Holy Cross; Brooklyn Polytechnic; Boston College; Providence College. He holds the Rumford Medal of the Royal Society, London, and the Franklin and Faraday Medals, the Lorentz Medal of the Royal Netherlands Academy, the Max Planck Medal (1950) awarded by the West Germany Physical Society, the Willard Gibbs Medal (Chicago, 1949), the Nichols Medal (1961), the Kendall Award (Miami, 1957), and the Priestley Medal of the American Chemical Society (1963); and was appointed Kommandeur des Ordens Leopold II in 1956.

Debye was a Visiting Lecturer at many universities – Columbia, California, Paris, Liège, Oxford, Cambridge, Harvard, Michigan, South California – and has been associated with scientific academies in many countries: Washington, New York, Boston, and Philadelphia in the United States of America; The Netherlands; Great Britain (the Royal Institute of Great Britain and the Royal Society, London); Denmark; Berlin, Göttingen, and Munich (Germany); Brussels and Liège (Belgium); Royal Irish Academy, Dublin; the Papal Academy, Rome; the Indian Academy, Bangalore and the National Institute of Science (India); the Real Sociedad Española de Fisica y Quimica and Academia de Ciencias, Madrid (Spain); and the Academies of Science of the U.S.S.R., Hungary and Argentina. The year 1936 saw the award of the greatest honour possible to him – the Nobel Prize for Chemistry.

Professor Debye is married to Mathilde Alberer and has a son Peter Paul Rupprecht (b. 1916) and a daughter Mathilde Maria (b. 1921), both married.

Chemistry 1937

WALTER NORMAN HAWORTH

«for his investigations on carbohydrates and vitamin C»

PAUL KARRER

«for his investigations on carotenoids, flavins and vitamins A and B_2»

Chemistry 1937

Presentation Speech by Professor W. Palmær, Chairman of the Nobel Committee for Chemistry of the Royal Swedish Academy of Sciences

Your Majesty, Royal Highnesses, Ladies and Gentlemen.

To the most important chemical compounds belongs a group of substances named carbohydrates. They have been so called because of their composition, which is such that they may be considered as built up by a combination of carbon and water – *hydrates* is the common terminology for chemical compounds in which water is a constituent. The least complicated forms of carbohydrates are the so-called monosaccharides, among which belongs grape-sugar, so designated because of its presence in the juice of grapes. The Latin name of sugar is *saccharum*; hence, the various types of sugar are also named saccharides. By a combination of particles – molecules – from the monosaccharides under separation from part of the water, complex saccharides are obtained, in the first place disaccharides, among which may be mentioned the well-known cane-sugar, and also milk-sugar and maltose. By continued combination more complex carbohydrates may be obtained, which have too been called polysaccharides, even though they have lost the properties of sweet taste and easy solubility in water. To these compounds belong, i.a., all kinds of starch, which constitute such an important part of our food, and also *cellulose*, the building material of the plants, which represents the most complicated form of the carbohydrates. While one molecule of grape-sugar is built up by 6 atoms of carbon, 12 of hydrogen, and 6 of oxygen, the number of atoms in one molecule of cellulose probably exceeds two thousand.

When the Nobel Prize in Chemistry was distributed for the second time, in the year 1902, it was awarded to the scientist of genius Emil Fischer, in recognition of his investigations partly concerning sugars and partly relating to caffeine and substances allied thereto.

This year the Royal Academy of Sciences has decided to attribute one half of the Nobel Prize in Chemistry to Professor W. N. Haworth of Birmingham in recognition of his researches concerning carbohydrates and vitamin C.

One may perhaps question if there remained much to be done within the domain of chemistry of the carbohydrates after the classical works of Emil

Fischer. This question must, however, be answered in the affirmative. To take only the case of monosaccharides of the type of grape-sugar, no less than 32 different forms are possible, all having the same chemical composition and containing an equal number of atoms in the molecule, but still differing from each other, this difference depending on the different arrangement of the atoms within the molecule. The possibilities are still more diverse when complex saccharides – the disaccharides – are considered, to say nothing of starch and cellulose, and these differences, in the case of the saccharides alone, small as they may appear, are yet of great interest, not only from a theoretical point of view, but also for the comprehension of the central role of the sugars in metabolism, as well as in their technical applications.

It is true that Haworth is not alone in having effected progress within this domain. He commenced his researches with his countryman Irvine, who has also produced eminent works relating to carbohydrates. Others, too, among them the Nobel Laureate in Chemistry this year, Professor Karrer, have made highly meritorious contributions. Among the works of Haworth, his researches regarding the different forms of grape-sugar and on the arrangement of the atoms in cane-sugar, maltose and milk-sugar, starch and cellulose, ought to be given special prominence.

Among the motives for the awarding of the prize are also mentioned, however, the researches upon vitamin C which have been made by this scientist and which stand in close relation to his work on the monosaccharides.

The vitamins represent substances which have lately attracted the greatest interest and about which, up till very few years ago, the public knew just as much – or as little – as the chemists. It had been found that certain mysterious substances were necessary, though only in very diminutive quantities, in connection with the foodstuffs proper – i.e. carbohydrates, fats, and proteins – together with certain mineral salts, for the growth and normal development of the animal body, and that a lack of these substances caused diseases of various kinds. The animal body itself, in general, is lacking in the capacity to produce these substances, which must therefore be supplied in a ready form from vegetables, or else be prepared within the body from other more complicated substances contained in the vegetable foodstuffs.

The discovery of the vitamins has already been honoured by the awarding of Nobel Prize in Medicine. In 1929 one half of such a prize was awarded to the Dutchman Eijkman in recognition of his discovery that the eating of polished or peeled rice produced the severe, chiefly tropical, disease called

beri-beri, while people eating unpeeled rice remained quite sound. Hence he reached the conclusion that a substance of the kind aforesaid, now described as the antineuritic vitamin, or vitamin B_1, was contained in the husk or peel of the rice. The other half of the Nobel Prize in Medicine was awarded in the same year to Hopkins in recognition of his discovery of the vitamins of growth, that is, the substances necessary for the growth of the animal body – contained for instance in milk – and of which one of the most important has now been identified with vitamin A. And today the Nobel Laureate in Medicine is awarded his prize, i.a., for his discovery in connection with the very same vitamin which had been made the subject of investigation by Haworth.

What has Haworth then accomplished within this domain? The answer may be thus formulated that he has, above all, made clear the chemical structure of vitamin C.

The chemical structure of substances is expressed by the so-called chemical formulas. By chemical analysis the percentage of the different elements – in this case of carbon, hydrogen, and oxygen – which enter into a compound may be ascertained. Further, the weight of the atoms of the different elements, expressed for instance in relation to the atom of hydrogen, has long been known, the hydrogen atom being the lightest of all the elements. It is likewise possible to determine the weight of a particle, or molecule, of a compound, expressed in the same measure. It is hence possible to indicate how many atoms of the different elements are entering into one molecule of the compound. Thus, the gross formula of the compound is obtained. This formula, in the case of vitamin C, is quite simple, considering that it represents a vitamin, viz.: $C_6H_8O_6$. This formula tells us that one molecule of vitamin C consists of 6 atoms of carbon, 8 of hydrogen, and 6 of oxygen. It also indicates that vitamin C may be conceived as having originated through the elimination of 4 atoms of hydrogen from one molecule of grape-sugar.

But it is possible to advance still further. By ingenious adjustment or speculation, reminding us somewhat of the play of a puzzle, only perhaps a little more intricate, a firm conception has been formed about the order in which the atoms combine. If we conceive an ultra-enlarged model of a molecule, taken at a certain moment – because the atoms are not at a standstill within the molecule – and place a white screen on the one side of the model, while the other is exposed to light, a shadow-figure, also called a projection, of the molecule is obtained on the screen, showing the position

of the atoms in their relation to each other. A formula which is intended to reproduce this situation, under the assumption that the atoms were placed on the same plane, is called a structural formula. Such formulas have proved capable of explaining with a high degree of clarity the properties of the compound, and the puzzle thus may be considered as having been solved.

In reality it is, however, hardly correct to suppose that all the atoms within a molecule should be placed on the same plane; if that were the case, even the largest molecules would have the shape of a leaf of paper, which is less than probable. There remains then their dispersion in space, the so-called configuration, which also may be expressed by a formula.

Such a formula for vitamin C has been proposed by Haworth and Hirst, as well as by von Euler and has been subsequently proved to be correct by Haworth.

Before entering upon the practical significance of knowing the chemical structure of a vitamin, I ought to say a word about the notable properties which characterize vitamin C – the terminology does not, of course, give any indication in this regard. But this vitamin was previously called the antiscorbutic vitamin on the ground that the lack thereof caused the disease of scurvy, so much dreaded by the polar explorers of earlier times. This disease appeared during periods when the members of these expeditions were compelled to live on badly preserved foodstuffs, whereas the danger has been obviated by the introduction of better food preservation and a supply of fresh vegetables. The chemical name is ascorbic acid. This indicates on the one hand that the substance is an acid, on the other hand that it has a counteracting effect on scurvy, the medical name of which is *scorbutus*; thus the word ascorbic acid is equivalent to anti-scurvy acid.

The knowledge regarding the constitution of a vitamin does not only possess a theoretical interest but is also of very great practical importance. On the one hand it may be found possible, by minor changes in the known composition which may be brought about in an artificial way, to produce compounds which in some cases may prove to be more suitable as medicine. And above all, it opens the way to the artificial production of the compound, a thing of very great importance in the case of vitamins which do occur in nature only in a state of very great dilution. Thus vitamin C is already produced on a technical scale and at a price very much lower than that of the natural product.

The Royal Academy of Sciences has decided also to award to Professor Paul Karrer in Zurich one half of the Nobel Prize in Chemistry this year

in recognition of his researches concerning carotenoids and flavins, and the vitamins A and B_2.

Thus these two scientists have both worked on another common field of research, the vitamins. As I have already endeavoured to elucidate at some length the importance of making clear the chemical structure of the vitamins, taking vitamin C as an example, I may be somewhat brief regarding the brilliant discoveries made by Professor Karrer.

The carotenoids form a group of yellowish-red colouring matters, widely dispersed within the vegetable kingdom, which have obtained their name from the carrot in which they were first observed. The French name of the carrot is known to be *carotte*, while *Karotte* is one of the German names thereof. Carotenoids occur in various other red or yellow parts of vegetables, such as tomatoes, hips, turnips. The examination of these numerous substances was commenced by Karrer ten years ago, and he has succeeded in making clear their chemical structure. The mother substance is in itself a hydrocarbon of very complicated composition, i.e. a chemical compound consisting only of carbon and hydrogen. Its molecule consists of no less than 40 atoms of carbon and 56 of hydrogen. Other carotenoids also contain oxygen, as is the case, for instance, with astacene, which gives the red colour to boiled crayfish and to the «cardinal of the sea», the lobster. The colour of saffron and of paprica is likewise due to carotenoids.

The splendid research concerning the carotenoids, made by Karrer, received its coronation, when it led to the isolation, the production in a pure form and the determination of the chemical structure of vitamin A. This vitamin, which had been known to exist from its biological effects already since 1906 and the synthesis of which in a pure form had been tried in vain in many laboratories all over the world, was successfully isolated by Karrer in 1931 from cod-liver oil, and it was the first of the vitamins of which the chemical structure was clarified. It forms a growth factor, i.e. a substance necessary for the growth of the body. In 1929 von Euler found the same property existing in the carotine itself, and it has been proved since then that this is dependent on the circumstance that carotine, that is the dyestuff of the carrot, is a substance from which the animal body can in itself produce the vitamin A, which has a somewhat less complicated structure. It is also a medicine, as it prevents the serious disease of the eye called «dry eye» or xerophthalmia. Hence vitamin A has received the name of axerophthol.

Some words now regarding Karrer's researches on flavins and on vitamin B_2, which were commenced in 1933. Flavins are natural substances of a light

yellow colour which often glisten, or fluoresce to the green. One of them is vitamin B_2, also called lactoflavin, which was discovered by Warburg and Christian in the yellow respiratory ferment, and which has also been disentangled in regard to its chemical structure by Karrer. It constitutes likewise a growth factor, and Karrer's method of producing this compound has led to a technical production of the substance, which is of great biological importance. It contains, besides carbon, hydrogen and oxygen and also nitrogen.

Karrer has thus succeeded in elucidating completely the nature of two of the vitamins, hitherto considered as so mysterious, and one of them is now produced artificially. A characteristic of this scientist is his open eye to the great and important problems as well as to their kernels, and the independent way in which he attacks the problems and pursues his new departures with the aid of his own methods.

There remain many questions to be studied regarding the way in which the vitamins cooperate in such processes of life as cannot be started without their presence.

A vitamin does certainly not produce the effect alone, however. The lactoflavin, for instance, combines, with the aid of phosphoric acid, with an albuminous substance, and only in this way the yellow respiratory ferment is formed. Its molecule contains about 200 times as many atoms as that of the vitamin itself. The yellow ferment is reckoned as belonging to the catalyzers, i.e. substances capable to accelerate a chemical reaction without undergoing any change themselves. Their action may be compared to that of a lubricating oil on a rusty machine. In this case the oxidation of certain substances present in the body is taking place, thus a kind of combustion, although of course much slower than for instance the burning of wood in a stove. We may perhaps compare the very effect of the vitamin to that of a key. A heavy door may thus resist the strongest blows and knocks, but can easily be opened by the aid of a small key – always provided that the right key is found.

The discoveries, which have now engaged our attention, touch upon the domain of Physiology as well as that of Chemistry, a circumstance which has found its expression in that they have been awarded Nobel Prizes in Medicine as well as in Chemistry. Often it is just within the borderland between two sciences, where efforts have been frequently made to establish demarcatory lines (although mostly in vain), that the important discoveries are to be found. In such cases it is evidently of small avail, generally speaking,

to try to decide, even with the aid of the greatest acuteness, to which field of science such discovery should be properly attributed. The principal thing is, however, that the discoveries are recognized, if such be their value, and the classification of the prize awarded is a question of minor importance. In the present case it may be said, nevertheless, that the discoveries which have been awarded a prize in Chemistry are on the whole more chemically accentuated in their character than those which have received the prize in Medicine. In all the cases, however, such discoveries may be said to have « conferred the greatest benefit on mankind » in accordance with the intentions expressed in the will of Alfred Nobel.

Professor Haworth. The Royal Swedish Academy of Sciences has resolved to adjudge to you and Professor Karrer this year's Nobel Prize in Chemistry in recognition, for your part, of your most important researches into carbohydrates through which another epoch in the chemistry of these substances has been completed, and for your investigation of the constitution of vitamin C which is now produced artificially.

It is with the most sincere gratification that I have the honour of conveying to you the congratulations of the Academy on this distinction and I request you now to receive the Prize from his Majesty the King who has been graciously pleased to consent to hand it over to you.

Professor Karrer. The Royal Swedish Academy of Sciences has decided to confer upon you and Professor Haworth this year's Nobel Prize in Chemistry. In this way the Academy wishes to express to you her recognition for your brilliant investigations on carotenoids and flavins, as well as on vitamins A and B_2. As a result of your work, the structure of a vitamin has for the first time been clarified. The structure of a second vitamin has also been cleared up, thus enabling its technical preparation.

I convey to you the congratulations of the Academy and request you to receive the prize from the hands of his Majesty the King.

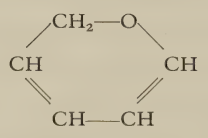
Walter N. Haworth

The structure of carbohydrates and of vitamin C

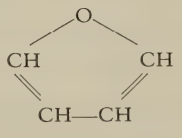
Nobel Lecture, December 11, 1937

The structure of carbohydrates and of vitamin C

Twenty years ago it could have been said that the wealth of natural products which comprise the carbohydrate group was bewildering in its complexity. Such materials as cellulose, glycogen, and starch seemed almost beyond the range of structural investigation. It was recognized that these products were built up somehow of simple sugars, particularly glucose. But our knowledge of the mode of combination of two or more glucose molecules was doubtful and insecure. This could scarcely have been otherwise inasmuch as it was not until 1925 that a precise structural model of any sugar was clearly and finally determined. The expressions used by Emil Fischer give us the stereochemical relationship of the hexoses and pentoses which he represented as open-chain aldehydes and ketones and these configurational conceptions will always be regarded as classical. It must now be said, however, that sugars of the hexose and pentose series, whether occurring as free isolated substances or assembled as the constituent parts of complex carbohydrates, conform to one of two simple structural models which are related either to pyran or to furan.



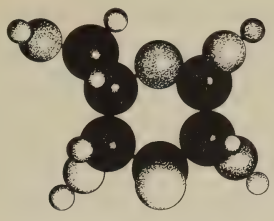
Pyran



Furan

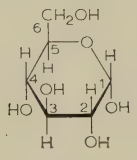
The model of glucose which I introduced in 1925 is represented in skeleton form as being built up of a ring of six atoms, five of these being carbon and one oxygen, together with an additional side-chain carbon atom. This I described as the pyranose form. When this model is clothed with its constituent oxygen and hydrogen atoms it then appears as represented in the second picture above where the model of β-glucose is portrayed. If we depart from this atomic representation and sketch a formula for α- and β-

Skeleton model of glucose

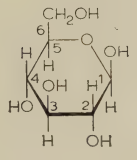


Model of β-glucose

glucose it will be best to have this model in mind and represent it by perspective formulae.



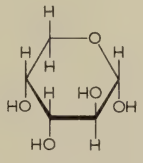
α-Glucopyranose

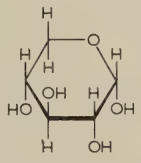


β-Glucopyranose

Other normal hexoses have been shown to conform similarly to this same structural plan. Thus the normal varieties of β-mannose, β-galactose, and β-fructose are illustrated below, all of them being pyranose forms, i.e. forms which are based upon the ring structure present in pyran. Similarly the normal pentoses have been shown to be pyranose in structure and their formulations are here given.

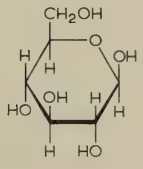
α-Arabo-pyranose

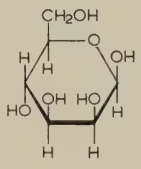




α-Xylo-pyranose

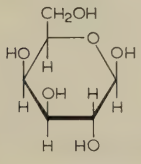
β-Gluco-pyranose

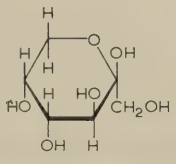




β-Manno-pyranose

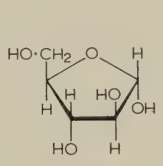
β-Galacto-pyranose



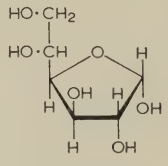


β-Fructo-pyranose

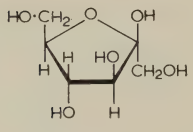
Much less stable forms of pentose and hexose are those which I have described as the furanose forms. Only the derivatives of these have been isolated as homogeneous crystalline substances, e.g. the ethyl- and methyl-glucosides which are hydrolysed with something of the order of 100 times the velocity of the normal methylglucosides. Yet it is in this form that certain sugars occur in a state of combination in Nature, particularly the pentose arabinose and the hexose known as fructose or lævulose. When these sugars are isolated they revert to the normal or pyranose forms which have six-atom rings.



α-Arabo-furanose



α-Gluco-furanose



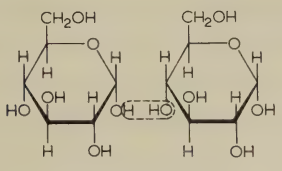
β-Fructo-furanose

It is clear that these simple sugars acquire wider significance when regarded as the building stones in such complex natural products as cellulose, starch, inulin, or the wood gum known as xylan. Much of my work has been devoted to an inquiry into the manner in which two or more sugars unite with one another or are found united in Nature in the disaccharides such as sucrose, maltose, cellobiose, gentiobiose, melibiose and others. From the picture of simple sugars which I have given it will be evident that there are several ways in which two glucose units may unite, by loss of water, through the intermediary of a common oxygen atom. Investigations conducted during the past 15 years have enabled us to build upon the speculations of Emil Fischer and to arrive at a precise picture for each of the disaccharides. The expression

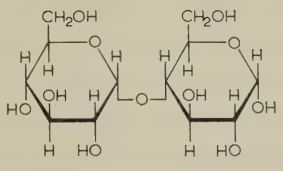
$$C_6H_{12}O_6 + C_6H_{12}O_6 = C_{12}H_{22}O_{11} + H_2O$$

merely indicates the union of two hexose residues with loss of water to give a biose. Any of the five hydroxyl positions present in a hexose such as glucose are available as a means of attachment to a similar glucose residue. Actually those bioses found in Nature do not exhaust all the possibilities which are available as a means of assembly of pairs of sugar units.

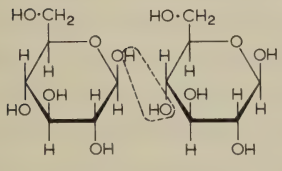
If we utilize a method of numbering the carbon atoms of a pyranose, beginning with the reducing group or potential aldehyde group in an aldose as No. 1, this will facilitate our reference to the various structures which apply to the known disaccharides. It must be remarked that the hydroxyl group attached to No. 1 position is located below the plane of the ring in the α-form and above the plane of the ring in the β-form and these two formulae are illustrated above. When we come to consider the mode of assembly of the pairs of glucose residues which occur in the representative bioses such as maltose and cellobiose, it is found that a unit of α-glucopyranose is linked with the hydroxyl at the 4th position of another glucose residue to give maltose, but on the other hand cellobiose is found to be derived from β-glucopyranose which is linked to a similar unit at the same 4th position.



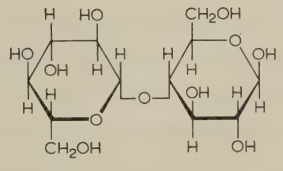
Union of two α-Gluco-pyranose molecules



α-Maltose



Union of two β-Gluco-pyranose molecules

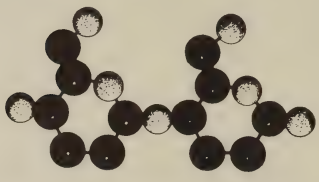


β-Cellobiose

This is illustrated in the formulae shown above. In the case of cellobiose it is seen that the active group at No. 1 position of one glucose unit is above the plane, and is united to a hydroxyl group below the plane of the ring in the second residue at position 4. To bring the rings into alignment in the final cellobiose formula shown on the right, one of these rings is now in-

verted or turned through 180°. Although the units participating in the union of maltose are structurally identical with those assembled in cellobiose yet these products are widely different in kind.

The difference lies entirely in the spatial arrangement of the left-hand formula indicating the α- or β-form of glucopyranose. This simple distinction furnishes the reason for the different entities of maltose and cellobiose.

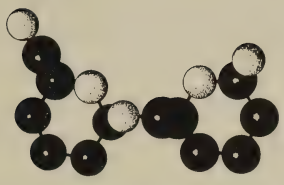


Maltose skeleton

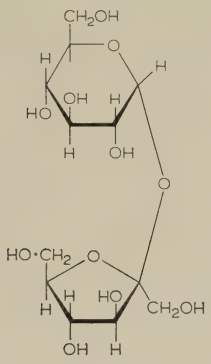
Cellobiose skeleton

This difference is fundamental and provides also a reason for the difference in identity of starch and cellulose. It is found that starch is based entirely on the maltose model inasmuch as maltose is obtained in high yield from starch. On the other hand cellobiose is the representative disaccharide derived from cellulose and it is the mode of linking obtaining in cellobiose which is repeated throughout the whole molecule of cellulose. These constitutional forms are seen more clearly in the atom models which I represent as the skeletons of maltose and cellobiose.

Other disaccharides exist in which the linking is different. For example, the mode of assembly of two glucose units combined through the hydroxyl positions at 1 and 6 is found to occur in gentiobiose, which is the biose present in the glucoside amygdalin. In the examples given we have seen that the assembly of pairs of hexose units is effected by the linking of the hydroxyl at position 1 of one unit with the hydroxyl in another unit at either position 4 or 6. Turning now to the important disaccharide, sucrose, we find that here two different hexose units are involved, namely, glucose and fructose, which are assembled as a pair through the union of the hydroxyl at position 1 in glucose with that at No. 2, which is the reducing position in this case, in the fructose residue. Sucrose is unique in its constitution inasmuch as in this example of a biose we find a pyranose, or six-atom ring form, linked with a furanose, or five-atom ring form, and as the reducing positions in each are utilized in their combination to a biose, sucrose becomes a non-reducing sugar. Probably for this reason it is more easily crystallized



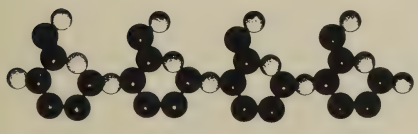
Gentiobiose skeleton



Sucrose

than the other bioses and we know it to be the most abundant, or the most easily available, of all pure organic substances.

From this rapid review of structural forms and of the modes of assembly of pairs of sugar units in a biose, let us now turn to illustrate similar experimental conclusions as to how more than two sugar molecules are assembled in various forms of carbohydrates. These formulations are based on the same kind of chemical proof as I have applied to the disaccharides, but in a review of this kind I propose to concern myself with results rather than with methods. Let us now take two pairs of maltose molecules and show how these are assembled in starch and glycogen and similarly how two cellobiose units are united as they appear in the cellulose chain. Thus we are able to approach to the constitutional picture representing starch and cellulose. Or if we envisage the procedure of adding repeating units of maltose to an ever lengthening chain we arrive at the model of starch and, by repeating a similar procedure with cellobiose, we represent repeating units as they occur in a very extended chain molecule in cellulose. Remarkable as the statement may appear it is nevertheless the case that these two models are structurally identical. They owe their differences to the two stereochemical forms of the same

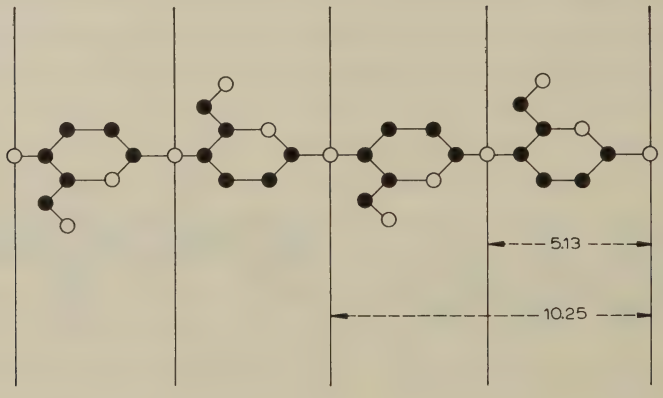


Two maltose units assembled as in starch

Two cellobiose units assembled as in cellulose

glucopyranose unit; as already stated, these are found to be α-glucopyranose in maltose and β-glucopyranose in cellobiose. The more symmetrical figure is that provided by the repeating pattern of cellobiose units. Here the side chain on each hexose appears alternately above and below in the picture, and this contrasts with the model shown for starch inasmuch as the side chain or 6th carbon atom occurs entirely on one side, a representation less symmetrical than that of cellulose. Moreover, the departure from the true linear arrangement is greater in the case of starch than of cellulose. The reason for this is apparent because in cellulose each alternate glucose unit is reversed and therefore any departure from the true linear direction is corrected in this model. We see therefore that in the structural representation for cellulose we have a reason for the occurrence of cellulose as a fibre in that its molecule approaches the rectilinear condition. Thus its conformation is more regular and provides a pattern which characterizes the X-ray diagrams for this substance. The diagram for starch is much less regular and less easy to interpret. Moreover there are other characteristic differences probably traceable to the continuous pattern formed by the assembly of α-glucose units in starch and to this we shall return. The cellobiose picture as determined by the classical methods of organic chemistry fits perfectly into the size of cell demanded by the X-ray diagrams, which fulfil every dimension of the repeating pattern of the cellobiose formula.

A question of particular moment is concerned with the length of the chain of repeating units in starch, cellulose, and glycogen. For it may now be said that glycogen has the same internal constitution as starch. On the other hand xylan or wood gum is constituted on a similar plan to cellulose except that it is built up of xylose units, largely, in place of glucose. Wisdom dictates



that in a problem of this complexity all the available polysaccharides should be studied together as a group. Information which may not be readily available from the study of one polysaccharide may be revealed by the study of another, and it is probable that a conclusion will be reached which is common to all of them. It is a reasonable supposition that Nature in building up polysaccharides follows a common plan. For this reason I have developed what is now known as the end-group assay of methylated polysaccharides as a preliminary to the study of the chain length. Unless these chains are constituted as continuous loops then there must be a terminal group which carries one more non-reducing hydroxyl than any of the intermediate units in the chain, or than the remaining end group which will terminate with a reducing unit. Our study of xylan has been important from this point of view. In xylan some 17 or 18 β-xylopyranose units are assembled in a chain which is terminated by one unit of arabofuranose. This latter can be easily removed by hydrolysis and there remains only a chain of xylose residues. In 1934 I pointed out that this picture of xylan was probably typical of other polysaccharides in that these chains of limited length aggregated to form a larger entity and the nature of the bonds effecting the union of adjacent chains was discussed. It was suggested that these might be either united by principal valency links or by some other type of bond such as that which is responsible for coordination. Whatever this kind of agency or link may be, I prefer to describe it as the polymeric bond and as such it may differ from ordinary valency bonds and may find currency in the whole field of polymeric substances.

In starch, for example, the individual chains terminate after 26 or 30 α-glucopyranose units and the chains are assembled by the same aggregative force as that just mentioned. It has been found possible to effect the reverse change of disaggregation in the case of starch. This was effected by mild acid treatment of the starch grains followed by acetylation and methylation. Very recently this observation has been confirmed by my former colleague E. L. Hirst who has isolated the methylated form of a single chain of 26 α-glucopyranose units. In the case of glycogen the chains differ from starch in being shorter in length and we have examined specimens of glycogen which contain continuous chains of both 12 and 18 α-glucose units. These chains again are interlinked by the polymeric bond to form a very large molecular complex showing a molecular weight of 1,000,000 or more.

The same experimental methods have been applied in order to gain an insight into the molecular size of cellulose. Here the complexity of the prob-

lem is very great. In 1932 I showed that, taking every precaution to avoid breakdown of cellulose, cotton linters could be acetylated under mild conditions and then methylated, by two treatments only with the reagents, to attain an almost completely substituted methylated specimen. This, by the method of end-group assay, contained one end group recognized as crystalline tetramethyl glucose for every 190 units of trimethyl glucose. The observation was made that the value of 100 to 200 β-glucopyranose units probably constituted the minimum length of chain in cellulose but that native cellulose untreated by chemical reagents would probably be found to possess still greater complexity. In this connection I suggested in 1935 that the molecular aggregate of cellulose may comprise an aggregation which not only increases the length of the chain, but also the width, by the lateral combination of adjacent chains. I pointed out that these factors must be recognized in any comparison of the molecular weight of cellulose determined by physical and chemical methods. All recent experiments in my laboratory have fully confirmed these conclusions. There can be no doubt that those forces which I describe as polymeric bonds are active in linking together adjacent chains of cellulose as in the case of xylan, glycogen, and starch. I do not share the view recently expressed that cellulose is constituted on the plan of a continuous loop of glucose units, this single loop being of a size to correspond with the high molecular weight found for cellulose by physical methods, although in my book on the constitution of sugars published in 1929 I suggested that this conception must be fully explored.

Time does not permit me to outline the range of facts which have been accumulated from our study of other polysaccharides such as inulin, mannan, and certain of the vegetable gums such as gum arabic, or gum acacia. But these experiments have thrown further light on the general problem of the molecular structure of complex carbohydrates.

Now, if I may, I should like to turn to another aspect of the subject of carbohydrates which brings us to the study of the constitution and synthesis of vitamin C.

The constitution and synthesis of vitamin C

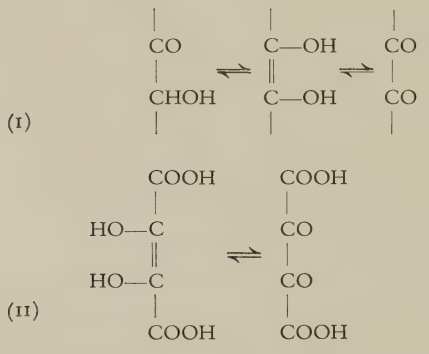
It will be recalled that in the course of his researches in 1928 Szent-Györgyi isolated from the adrenal cortex and also from orange juice and cabbage juice, a highly reducing substance which has many of the properties of a

carbohydrate. This substance had been named hexuronic acid in virtue of its acidity and strong resemblance to highly reactive sugar acids. It was crystalline, having melting point 192° and $[\alpha]_D + 23°$ in water; it was easily affected by oxidizing agents, and was capable of undergoing reversible oxidation by iodine or phenol indophenol. The molecular formula was established as $C_6H_8O_6$, and before any question of its relationship to a vitamin arose, Professor Szent-Györgyi paid me a visit in the University of Birmingham and invited me to investigate the constitution of this highly interesting substance.

Soon its possible connection with vitamin C appeared probable from the experiments of Szent-Györgyi and Svirbely and of Tillmans and also of Waugh and King. At this stage larger quantities of the material were prepared by Szent-Györgyi, first of all from adrenal cortex and later from Hungarian paprika, a richer and much more convenient source. On the suggestion of Professor Szent-Györgyi and myself, the name of the substance was changed from that of hexuronic acid, which was not distinctive, to that of ascorbic acid. It had been shown by Szent-Györgyi that the antiscorbutic activity was due to the substance itself and not to a contamination of the material with some more potent substance. Moreover, we prepared the primary oxidation product of ascorbic acid and this was found by Hirst and Zilva to be as active physiologically as the original ascorbic acid; and further, it was shown that the acid regenerated by the reduction of the oxidized material was still fully active. These observations showed that Tillmans' hypothesis concerning the reversible oxidation of vitamin C was indeed correct and they served also to explain the earlier observations of Zilva on the so-called « reducing factor ». Further evidence that ascorbic acid was identical with vitamin C came from investigation of the potency of samples prepared from different sources; and the observation that synthetic ascorbic acid prepared from completely inactive materials had the same degree of physiological activity as the natural substance, furnished final and incontrovertible proof.

Constitution of ascorbic acid. Ascorbic acid is a monobasic acid, giving well-defined salts of the type $C_6H_7O_6M$. It is a powerful reducing agent and its oxidation can be effected in stages, the first of which requires the equivalent of one atomic proportion of oxygen for each molecule of ascorbic acid. When oxidation is arrested at this stage the product can be reduced quantitatively to ascorbic acid by reducing agents such as hydriodic acid or hydro-

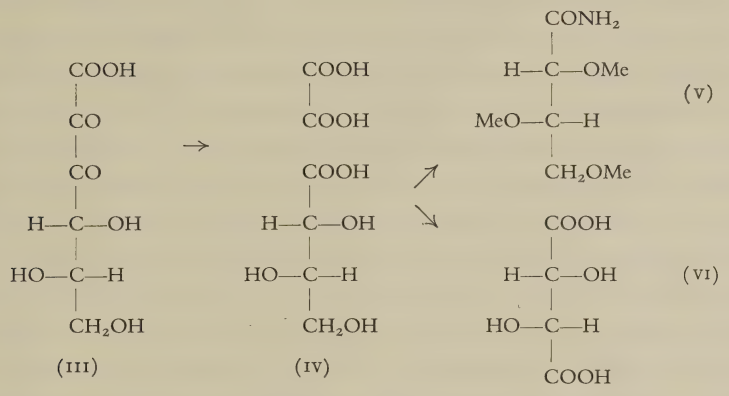
gen sulphide. Ascorbic acid is specially sensitive to oxidation by gaseous oxygen in the presence of minute traces of copper as catalyst, but in these circumstances the reaction proceeds beyond the reversible stage and involves destruction of the molecule. Ascorbic acid reacts readily with phenylhydrazine giving a product having the composition of an osazone. The presence of at least one keto group capable of undergoing enolization is thus confirmed and the character of the ultraviolet absorption spectrum (intense band at λ 245 mμ in acid solution) is in full agreement with this. Furthermore, the intensity of the absorption suggests that conjugated double bonds are present in the molecule. The above mentioned properties pointed to the presence in ascorbic acid of the group (I) and an exact analogy is provided by dihydroxymaleic acid (II) which displays absorption similar to that of ascorbic acid and undergoes reversible oxidation by iodine in acid solution.



Another property of ascorbic acid which was known at an early stage in the investigation and played an important part in the elucidation of the molecular structure was the unusual flatness of the molecule revealed by crystallographic and X-ray examination carried out in my laboratory by Dr. Cox. By attention to this criterion a choice could be made between alternative structural formulae which, at the commencement of the investigation, appeared to satisfy the requirements of the known chemical transformations.

Our observation that ascorbic acid could be transformed almost quantitatively into furfural provided strong evidence that the molecule contained a straight chain and not a branched chain of carbon atoms. Further evidence of this, and insight into the stereochemical relationships of ascorbic acid were obtained from a study of the oxidation, by sodium hypoiodite, of the primary (reversible) oxidation product. Two substances were obtained in al-

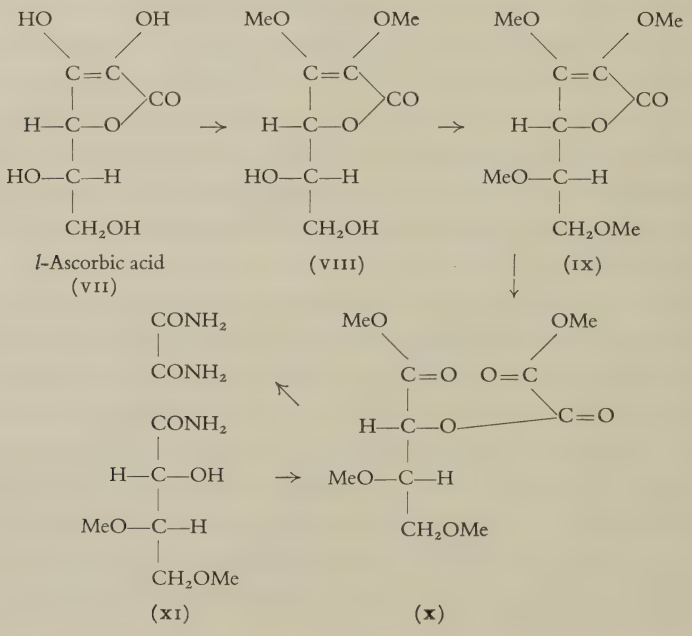
most quantitative yield, namely oxalic acid and *l*-threonic acid (IV), the identity of the latter being established by its transformation into trimethyl *l*-threonamide (V) and into *d*-tartaric acid (VI). These facts establish the conclusions that in alkaline solution the primary oxidation product of ascorbic acid reacts as a salt of the acid (III) and that ascorbic acid is related stereochemically to *l*-gulose.



An important observation was that, when newly formed, the primary reversible oxidation product from ascorbic acid does not possess acidic properties but behaves in all respects as a lactone, which develops acidity when kept in aqueous solution. It followed that the acidic character of ascorbic acid is due to an enolic hydroxyl group and not to a free carboxyl group and, in order to determine the structure of ascorbic acid, it remained only to discover the nature of the lactone ring in the primary oxidation product. The main features of the constitution of ascorbic acid were now established and its formulation as a lactone of 2-keto-*l*-gulonic acid, capable of reacting in various tautomeric modifications, was first announced from the University of Birmingham, early in 1933.

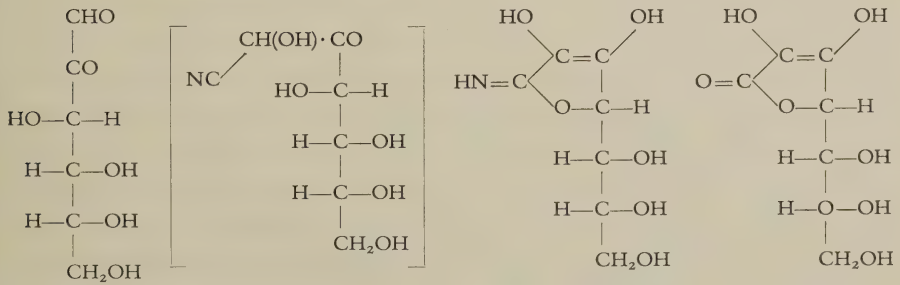
The elucidation of the nature of the lactone ring followed from a study of the oxidation product obtained when tetramethylascorbic acid reacts with ozone. It had been shown by Micheel that the dimethyl derivative of ascorbic acid, obtained by Karrer by the action of diazomethane, gives a di-*p*-nitrobenzoyl derivative and that the latter reacts with ozone giving a neutral ester containing the same number of carbon atoms as the unoxidized material. It followed that a ring system must be present in ascorbic acid, but the products obtained on hydrolysis of the neutral ester (oxalic acid and *l*-threonic acid) did not permit of deductions being made concerning the na-

ture of the ring, and the interpretation at that time advocated by Micheel was invalid in that it involved the presence of a free carboxyl group in ascorbic acid. By reference to the accompanying formulae it will be seen that by application of a similar method of oxidation to fully methylated ascorbic acid the nature of the ring system can be determined with certainty. It was found that dimethylascorbic acid (VIII) was readily converted into the corresponding tetramethyl derivative (IX) by the action of silver oxide and methyl iodide, and that this on treatment with ozone gave rise to a neutral ester (X) which reacted with ammonia giving oxamide and the amide of 3:4-dimethyl-*l*-threonic acid (XI). The presence of a hydroxyl group in the α-position in the latter substance was proved by the observation that the amide gave a strong positive Weerman reaction (formation of sodium cyanate by the action of sodium hypochlorite on the amide). It follows immediately that in ascorbic acid, in dimethylascorbic acid, and in tetramethyl ascorbic acid, the lactone ring is of the γ-type and engages the hydroxyl group attached to the fourth carbon atom of the chain. Ascorbic acid is therefore to be represented by (VII). If, on the other hand, ascorbic acid had contained a δ-lactone ring the products, obtained by the action of ammonia on the neutral ester formed by ozonization, would have been oxamide and 2:4-dimethyl-*l*-threonamide and the latter amide would not have under-

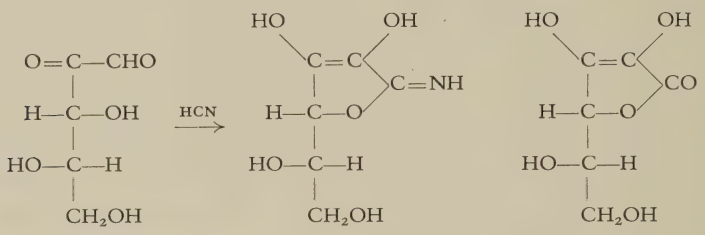


gone the Weerman reaction. The structure (VII) (enolic form of 2-keto-*l*-gulonolactone) is in full agreement with all the chemical properties of ascorbic acid and, when an atomic model of this constitution is built up, it is seen that the structure is almost flat and its dimensions account satisfactorily for the crystallographic and X-ray observations.

The synthesis of ascorbic acid. The two principal methods which are now available for the synthesis of ascorbic acid and its analogues are: (a) addition of hydrogen cyanide to an osone followed by acid hydrolysis of the addition compound, and (b) the re-arrangement of 2-keto-3:4-dihydroxy-acids or their esters. Method (a) suffers from the disadvantage that it requires osones as starting materials, and when these are available it is a powerful and certain method which has been utilized for the preparation of many analogues of ascorbic acid. Moreover, it was the method employed simultaneously by Reichstein and by Hirst and myself, in the first synthesis of the *d*- and *l*-isomerides of ascorbic acid. The mechanism of the reaction has been the subject of detailed investigation and it will be illustrated by reference to the synthesis of *d*-gluco-ascorbic acid. The first stage of the synthesis from glucosone (XII) results in the formation of $C_7H_{11}O_6N$, a crystalline addition product which displays a strong absorption band at λ 275 mμ. The properties of this substance show that it is not the open-chain cyanohydrin (XIII) but the cyclic imino-compound (XIV) which exists in aqueous solution as a neutral internal salt, evidence on this point being obtained from studies of the optical rotatory dispersion of the substance in neutral and in acid solution (when the ionisation is suppressed). Similar cyclic bodies have been obtained in the course of synthesis of other analogues of ascorbic acid and the reaction appears to be a general one. The intermediate cyclic-imino body (XIV) possesses many of the characteristic properties of ascorbic acid (e.g. intense



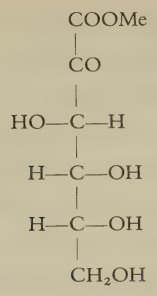
absorption band, oxidation by iodine in acid solution) and on hydrolysis by aqueous acid the imino group is removed and gluco-ascorbic acid (XV) is produced. The latter substance possesses the characteristic ring system of ascorbic acid, and displays chemical properties (and an absorption spectrum) closely similar to those of natural ascorbic acid. The synthesis of natural *l*-ascorbic acid (vitamin C) proceeds in a similar way from *l*-xylosone (XVI) which is obtainable from *d*-galactose as the outcome of the following series of transformations: *d*-galactose → *d*-galactose-1:2,3:4-diacetone → *d*-galacturonic acid-1:2,3:4-diacetone → *d*-galacturonic acid → *l*-galactonic acid → *l*-galactonamide → *l*-lyxose → *l*-xylosazone → *l*-xylosone.



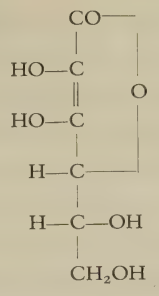
l-Xylosone (XVI) *l*-Ascorbic acid (VII)

Several analogues of *l*-ascorbic acid have also been synthesized by the above-mentioned method. It may be observed that the nomenclature adopted for convenience of reference derives the name of the substance from that of the osone used in the synthesis.

In the preparation of *l*-ascorbic acid it is advantageous to avoid the use of *l*-xylosone which is not easily accessible. By application of the second mode of synthesis notable advances have been made in the ease of preparation of synthetic vitamin C. This method was first applied by H. Ohle in the preparation of *d*-arabo-ascorbic acid (XVIII) from 2-keto-*d*-gluconic acid. The acid, and more particularly the methyl ester (XVII), undergoes ring closure and isomerization under a variety of conditions, amongst which the action of sodium methoxide may be referred to as of special importance, and the resulting substance possesses the ring system of ascorbic acid. In the case of natural ascorbic acid the necessary keto-acid is 2-keto-*l*-gulonic acid (XXII) which can be readily obtained, as shown by Reichstein, from *l*-sorbose (XX) by oxidation of sorbose diacetone (XXI) and subsequent removal of the acetone residues. *l*-Sorbose in turn is now available in quantity by the bacterial oxidation of *d*-sorbitol (XIX).

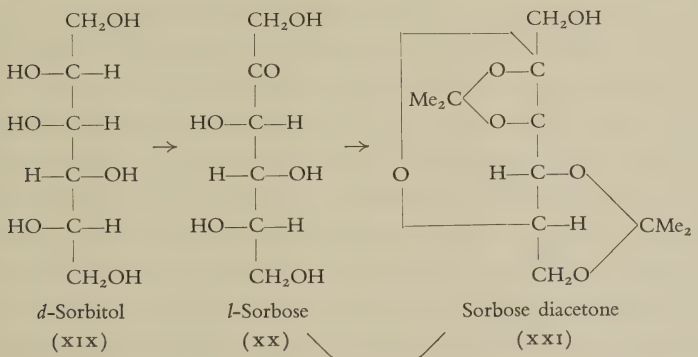


Methyl 2-keto-*d*-gluconate
(XVII)



d-Arabo-ascorbic acid
(XVIII)

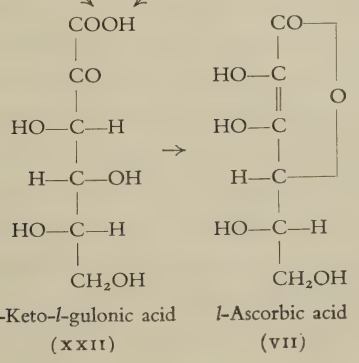
A still simpler method for the synthesis of *l*-ascorbic acid consists, as I have shown by my experiments, in the direct oxidation of *l*-sorbose which like *d*-fructose, is specially sensitive to oxidation at the primary alcoholic group at C_1. When oxidized under carefully controlled conditions by nitric acid *l*-sorbose (XX) is transformed directly into (XXII), and the methyl ester of (XXII) gives the sodium salt of *l*-ascorbic acid when treated with sodium methoxide. In a similar way *d*-fructose gives rise to 2-keto-*d*-glu-



d-Sorbitol
(XIX)

l-Sorbose
(XX)

Sorbose diacetone
(XXI)



2-Keto-*l*-gulonic acid
(XXII)

l-Ascorbic acid
(VII)

conic acid, the methyl ester of which yields the sodium salt of *d*-arabo-ascorbic acid (XVIII) on treatment with sodium methoxide.

That the distinguishing feature of ascorbic acid and its analogues, in so far as absorption spectra and chemical properties are concerned, lies in the enolic double bond, may be illustrated by reference to the work of H. von Euler and C. Martius on reductone (hydroxymethylglyoxal, CHO.C(OH) =CHOH) which resembles ascorbic acid chemically and in its absorption of light, and is strongly acidic without possessing a carboxyl group (Norrish and Griffiths).

Biography

Walter Norman Haworth was born at Chorley, Lancashire, on March 19, 1883. He attended the local school until the age of fourteen when he joined his father, Thomas Haworth, to learn linoleum design and manufacture. His interest in chemistry was aroused through the use of dyestuffs in his work and his thirst for further knowledge led him to seek private tuition in Preston. This coaching enabled him to pass the entrance examination of the University of Manchester and in 1903 he entered the Chemistry Department as a pupil of W. H. Perkin, Junior. He graduated with first class honours in 1906 and after three years research he went, on a scholarship, to Wallach's laboratory at Göttingen. He received his doctor's degree in 1910 and returned to Manchester to be awarded his D. Sc. degree in 1911–these qualifications were gained in the minimum time possible.

In 1911, Haworth took an appointment as a demonstrator at the Imperial College, London and in 1912 he moved to St. Andrews, Scotland, as Lecturer and Reader in Chemistry. In 1920, he was called to the Chair in Chemistry at the University of Durham and in the following year succeeded Phillips Bedson as Director. Haworth was appointed Professor and Director of the Department of Chemistry in the University of Birmingham in 1925 and he remained in this position until his retirement in 1948, becoming Dean of the Faculty of Science and acting as Vice-Principal during 1947–1948. Sir Norman was active in retirement, serving on many Boards and Committees; he represented the Royal Society at the Seventh Pacific Science Congress in New Zealand during February, 1949. He was knighted in 1947.

Haworth's early researches, initially with Perkin, involved investigations on the constitution of terpenes and in 1912 he synthesized sylvestrene. At St. Andrews, in association with T. Purdie and J. C. Irvine, he turned his attention to carbohydrates, extending Emil Fischer's method of reacting sugars with methanol to an elegant preparation of methylated derivatives which were, in turn, used to characterize the constitution of sugars.

During the First World War, Haworth organized the laboratories at St. Andrews for the production of fine chemicals and drugs; after the war he

returned once more to his carbohydrate investigations. By 1928, he had evolved and confirmed, among others, the structures of maltose, cellobiose, lactose, gentiobiose, melibiose, gentianose, raffinose and the glucoside ring structure of normal sugars. He studied lactones from sugars and co-related structure with optical rotatory powers. His method for the determination of chain length in methylated polysaccharides, an important structural problem, helped to settle the basic features of the starch, cellulose, glycogen, inulin and xylan molecules.

Following the synthesis of ascorbic acid, which considerably cheapened commercial production, Haworth's later researches contributed greatly towards further co-ordination of the chemical, physical and biological, problems concerned with bacterial polysaccharides.

Haworth wrote numerous scientific papers and contributed to *Advances in Carbohydrate Chemistry*. His book *The Constitution of Sugars* was published in 1929.

Haworth was President of the Chemical Society (1944–1946), and Fellow (1928), and Vice-President (1947–1948) of the Royal Society. He received honorary science degrees from the Universities of Belfast, Zurich and Oslo, honorary Doctor of Law, University of Manchester, and foreign memberships of nine foreign scientific academies. He was the Longstaff Medallist (Chemical Society), 1933; Davy Medallist (Royal Society), 1934, and Royal Medallist, 1942.

In 1922, Haworth married Violet Chilton, second daughter of Sir James Dobbie, LL.D., F.R.S. They had two sons.

He died suddenly on March 19, 1950.

Paul Karrer

Carotenoids, flavins and vitamin A and B_2

Nobel Lecture, December 11, 1937

In the last few decades chemical research has been divided in the main into two directions; one part aims at the investigation of the structure of the atom in the widest sense, the other at the elucidation of the composition of the living cell and its chemical reactions. The first direction has availed itself in many ways of entirely new methods of investigation, which are essentially of a physical nature. Biochemical research was able to base itself so far in the main on the methods of classical chemistry, which certainly have been improved and developed in an extraordinary manner.

Progress in methods which modern biochemistry can no longer dream of doing without, are the selective adsorption processes of Willstätter, separation by the ultracentrifuge of Svedberg, and chromatographic analysis by Tsvett, by the use of which it is now possible to separate mixtures of substances which were previously inextricable. Chromatographic analysis, in particular, which is based upon filtration of the solution of the mixture of substances through an adsorption column, in which the more easily adsorbed substances are retained in the upper part of the tube, with the substances more difficult to adsorb being retained in the lower part, operates in a similarly complete manner like a prism, which divides the white light into the individual colours of the spectrum. Thanks to these efficient separation processes our picture of the composition of plant and animal cells is today essentially more complicated than it was a few years ago, and it cannot be doubted that to later generations there will be revealed an even greater diversity and non-uniformity of the living cell.

The blue and red pigments of blossoms and berries, the anthocyanins, which were formerly thought to be uniform and characteristic for the various plants concerned, have been shown by later investigations to be mixtures of many closely related substances. There is indeed not one flower, not one berry, which owes its colouration to a single anthocyanin. Similar conditions apply in another group of natural pigments, the carotenoids, about which I have the honour to speak today. In the well-known book by L. S. Palmer on carotenoids which was published in 1922, only six carotenoids are

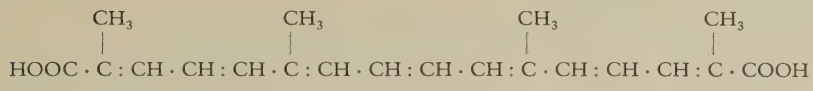
described which had been crystallized and analysed (carotene, lycopene, xanthophyll, lutein, fucoxanthin, and rhodoxanthin). Bixin was also known at that time. Until four years ago the number of these naturally occurring pigments had risen to 15; today we know already some 40 natural pigments of this group, the isolation of which has only been made possible by the new methods of separation.

Attention has been paid to the carotenoids in more recent research, not only because of their unique structure, but also because of their close relation to the vitamins, as some carotenoids are provitamins of vitamin A and are transformed into this vitamin in the animal organism. Investigation of the structural constitution of the vitamins started from carotene; when it was possible, in 1930, to establish the correct constitutional formula for β-carotene, a structural formula for any other vitamin or provitamin was not yet known. Shortly afterwards, in 1931, it became also possible to elucidate the constitution of vitamin A itself, and thus to obtain the first insight into the structure of a vitamin. We may perhaps remember that scarcely ten years have elapsed since the time when many research scientists doubted the material specificity of the vitamins, and were of the opinion that a special state of matter, a special colloidal character, was the cause of the peculiar vitamin effects which had been observed.

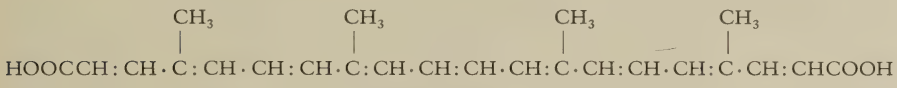
Carotene and its relatives are polyenes; they contain numerous conjugated double bonds in their molecules. We discovered this characteristic structural principle for the first time when investigating the saffron pigment, crocetin. As examples of the molecular structures of such polyenes I give here the formulae of crocetin, bixin (norbixin), the tomato pigment lycopin and β-carotene (see opposite page).

To the constitutionally clarified carotenoids there also belong α- and γ-carotenes, the second yellow pigment xanthophyll, whose wide distribution in the animal kingdom has been demonstrated by Lönnberg in particular, and also zeaxanthin from maize and many other fruits, the pigment of lobsters and many other crustacea, astacin, the paprika pigment capsanthin, cryptoxanthin, and many others.

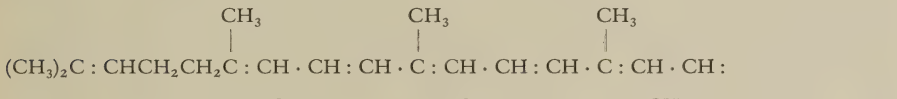
What is striking in the above structural formulae is not only the abundance of conjugated double bonds, unknown previously in any other natural substances, but the fact that the carotenoid molecules are composed of isoprene residues. This applies for all carotenoids which are therefore to be recognized as relatives of the terpenes, camphor, and rubbers. Furthermore, the symmetrical character of the above four formulae is striking; they are composed



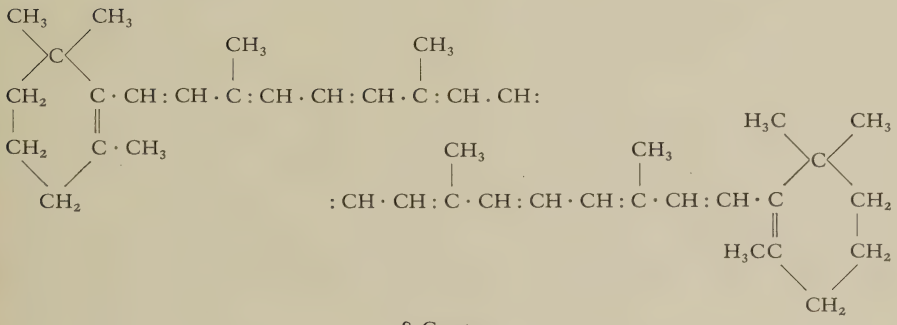
Crocetin



Nor-bixin Bixin



Lycopin



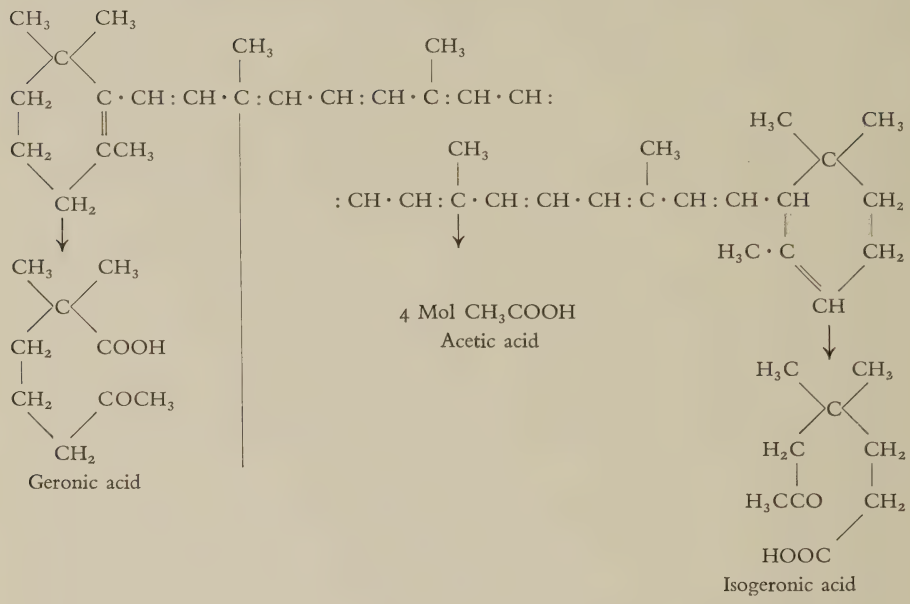
β-Carotene

of two equal halves, and so are centro-symmetrical – both ends of the molecule show the same structure. This structural principle, which we first recognized in the tomato pigment lycopin and then in carotene, later proved to be realized in other branches of terpene chemistry and was applied by various research workers with success in the derivation of structural formulae.

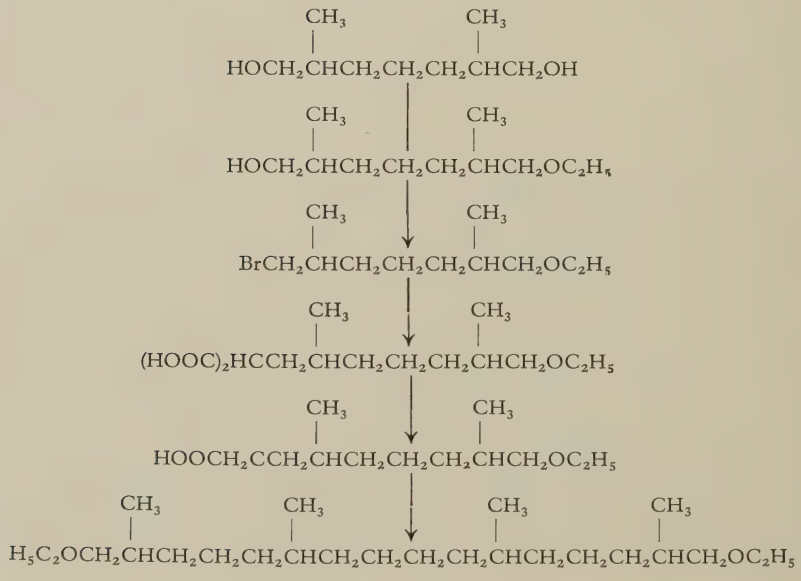
The structural formulae of the above-mentioned four carotenoids have been proved partly by decomposition reactions and partly by synthesis of their perhydro-derivatives.

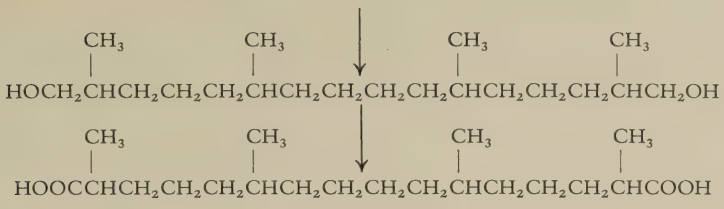
Two examples of this type are shown in the following structural formulae, one showing constitutional determination by decomposition and the other by synthesis.

Oxidative decomposition of α-carotene



Synthesis of perhydrocrocetin





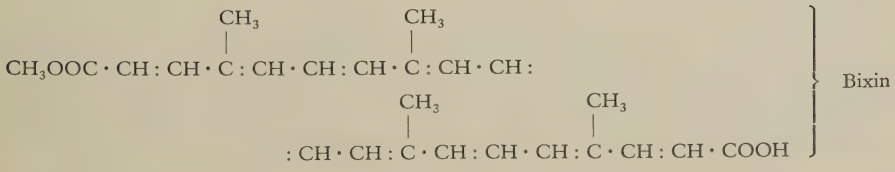
Perhydrocrocetin

However, the theory now allows us to foresee furthermore for each individual carotenoid extraordinarily numerous stereoisomeric forms, since at each individual double bond the substituents can be arranged either in *cis*-position or *trans*-position, whereby even two modifications of the *trans*-arrangement must be taken into consideration. Diagrammatically the three extreme cases (continuous *cis*-form, continuous attenuated *trans*-form, and continuous compressed *trans*-form) can be represented as follows:

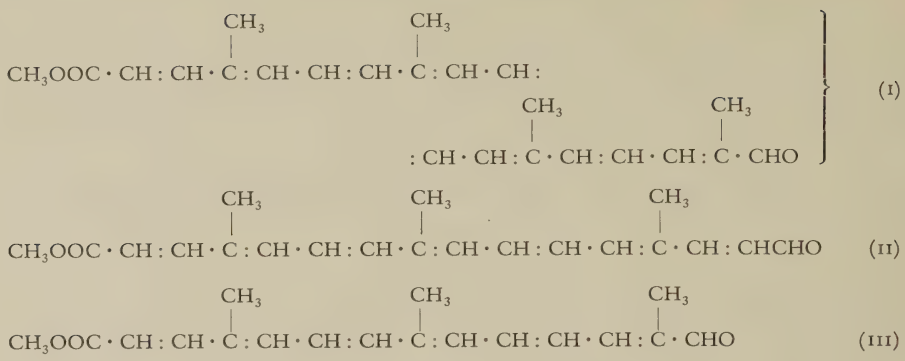
cis-form attenuated *trans*-form compressed *trans*-form

Theoretically a very large number of stereoisomers can be imagined by combining *cis*- and *trans*-arrangements. As in many other cases, however, Nature has made only slight use of these possibilities. Up to the present we know only two carotenoid pigments in which this *cis-trans*-isomerism is realized. These are bixin and crocetin, which occur in both forms as unstable and stable isomers.

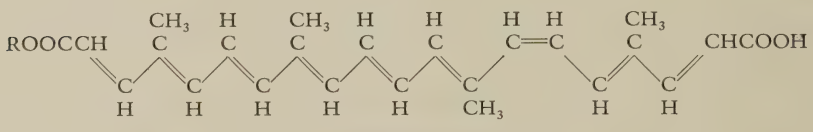
Despite the wealth of possibilities of isomerism which are available here, it can be established with great certainty, in the case of the unstable and stable bixin, which double bond is responsible for the occurrence of the two isomers. It is possible to decompose the polyenes by permanganate oxidation in stages to aldehydes in the sense that one double bond after another is oxidized. In this way the aldehydes I to III were obtained from unstable bixin:



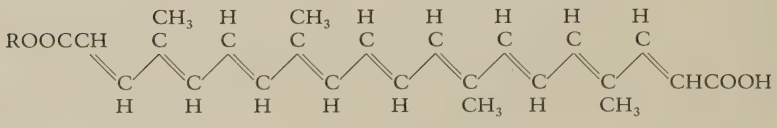
Bixin



In the same way decomposition of stable bixin yields aldehydes of structures I to III. Whereas the compounds III are identical in both cases, the aldehydes I and II obtained from unstable and stable bixin proved to be different; they are *cis-trans*-isomers. From this it can be seen that the stereoisomerism of the two natural bixins is very probably based on the different configuration of the third double bond, counted from the free carboxyl.* If a *trans*-form is assumed for the remaining double bonds (which for various reasons is not improbable, though not proved), then the differences in structure of the two isomeric bixins can be expressed by the following formulae:



Unstable bixin

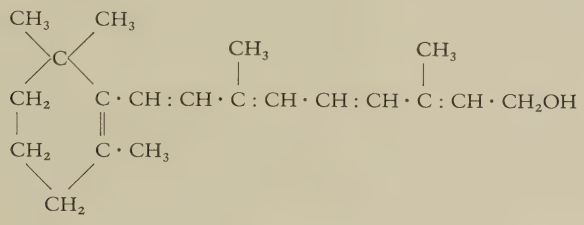


Stable bixin

* An objection to this conclusion could be brought forward, viz. that a labile apo-3-norbixinal methyl ester (Formula III), in contrast to the labile apo-1-norbixinal methyl ester and apo-2-norbixinal methyl ester (Formulae I and II), could rearrange *spontaneously* to a stable form under the conditions of the oxidation.

Even fine stereochemical details of such complex structural molecules are thus experimentally accessible to test and clarification.

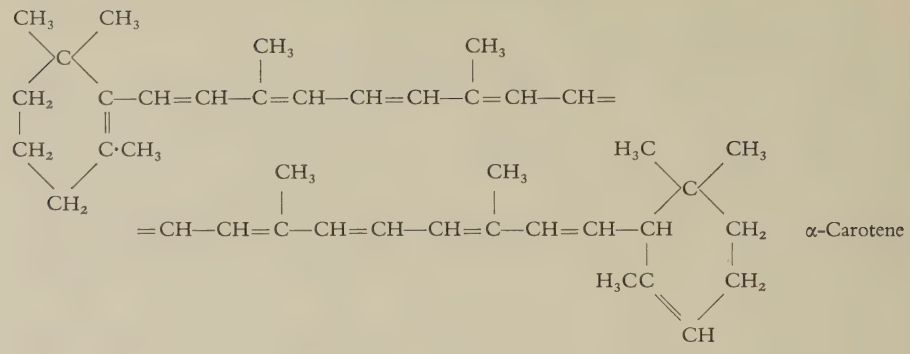
Reference to the close relationship of β-carotene to vitamin A has already been made. H. v. Euler recognized that carotene can replace vitamin A in experiments on animals, and Th. Moore proved that in the animal organism it is transformed into vitamin A. These near relationships became understandable when we succeeded in isolating and constitutionally elucidating vitamin A. The structural formula, which is proved by a synthesis of the perhydro-vitamin A, shows that the compound contains half of the carbon skeleton of β-carotene and from this, by splitting at the central double bond, the result must have been:



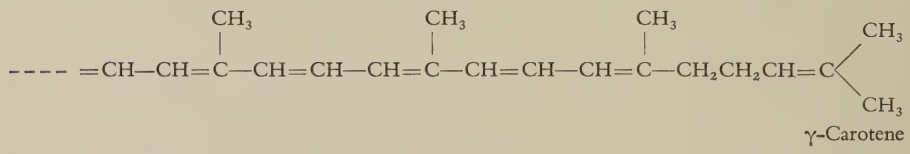
Recently this compound was given the name of axerophtol.

It appeared now to be of interest to establish whether still further carotenoids, besides β-carotene, could be decomposed through the animal organism, presumably through its liver tissue, to axerophtol. Investigation of this problem, which was carried out together with H. v. Euler, led first of all to the recognition that this does not hold true for most other natural carotenoids. Substitution by OH or keto groups, splitting of the carbon ring of β-carotene, etc., leads to a complete disappearance of the vitamin A effect. Besides β-carotene, in whose molecule the unsubstituted carbon skeleton of vitamin A occurs twice, those carotenoids proved still to be effective which contain the carbon skeleton in the unsubstituted form at least once. Pigments of this kind are α-carotene, γ-carotene*, cryptoxanthin*, echinenon**, a β-carotene oxide, dihydro-β-carotene, dihydro-α-carotene, diiodo-β-carotene, β-semicarotinone* and also β-apo-2-carotinal and β-apo-4-carotinal. The structural formulae of some compounds of this provitamin group show their close constitutional relationships to vitamin A:

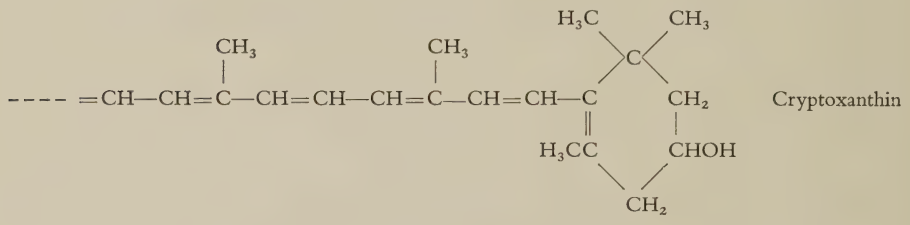
* R. Kuhn *et al.*
** E. Lederer



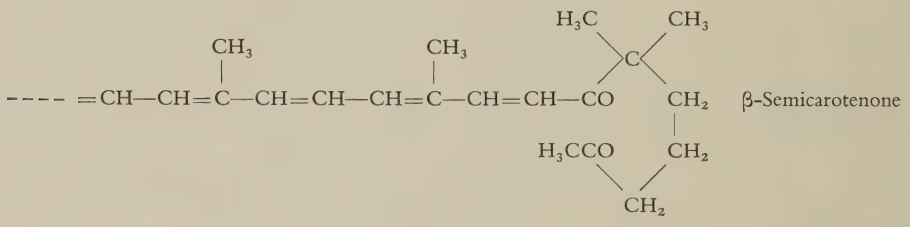
α-Carotene



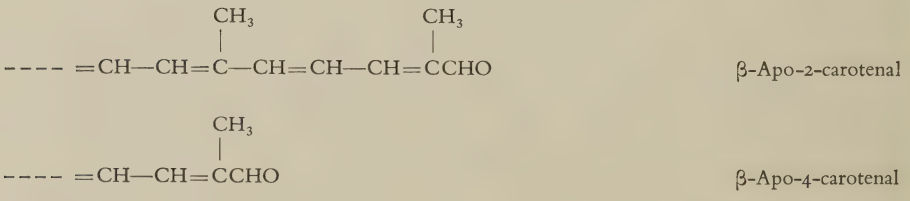
γ-Carotene



Cryptoxanthin



β-Semicarotenone



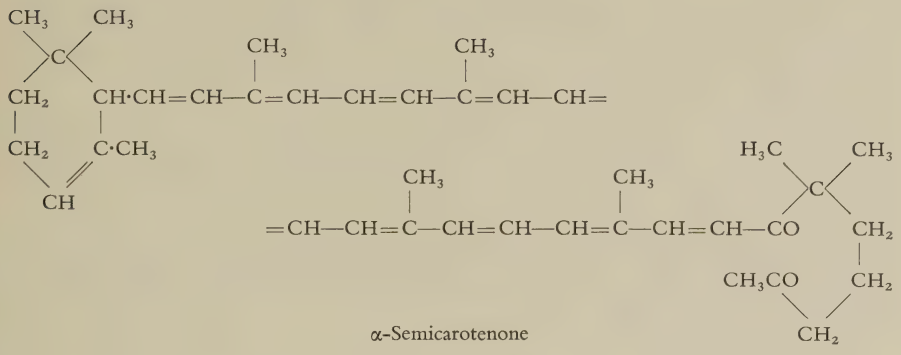
β-Apo-2-carotenal

β-Apo-4-carotenal

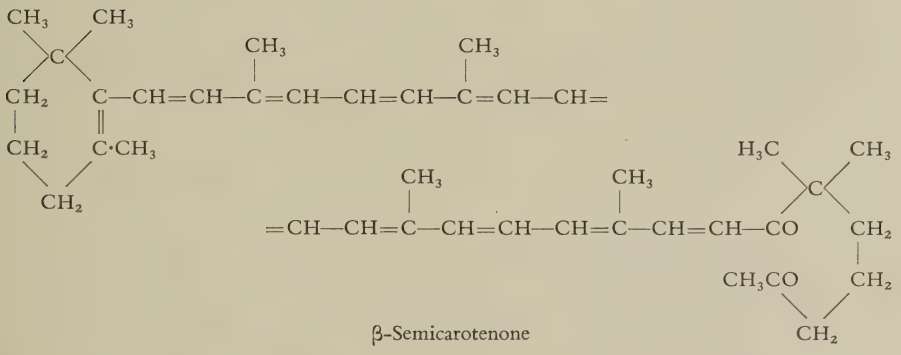
The last three of these provitamins are synthetic products, which have been formed by oxidative splitting at the first, second, or fourth double bond of the carotene molecule.

If a single double bond has changed its location in the carbon skeleton

characteristic for vitamin A, it is sufficient to neutralize its action as provitamin A. In this way α-semicarotenone, which differs from effective β-semicarotenone by displacement of the double bond in the carbon ring, proved to be quite ineffective:



α-Semicarotenone



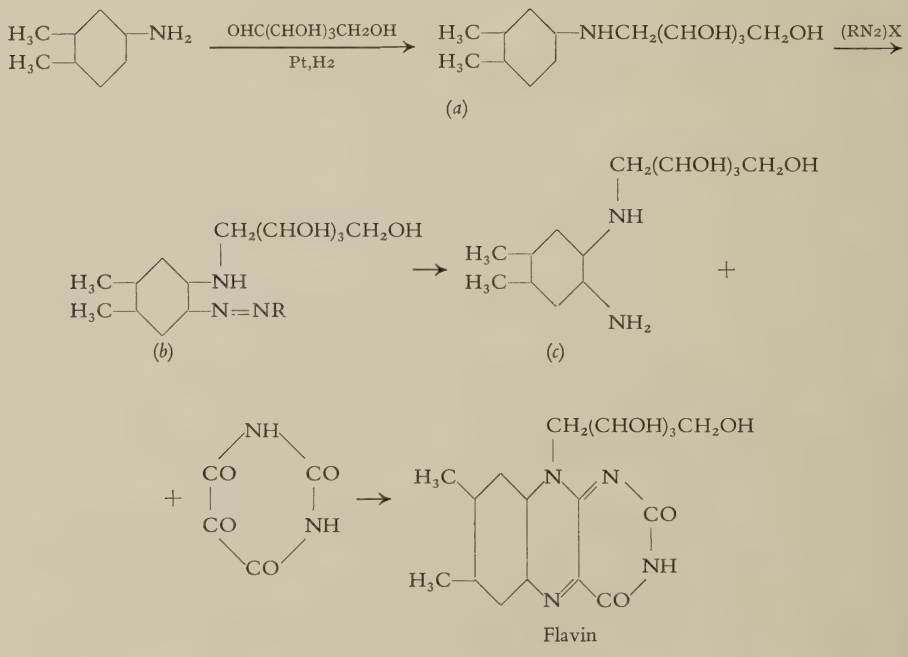
β-Semicarotenone

The action of vitamin A is consequently extraordinarily specific and bound to a quite definite structure. Today it is possible to show the atom arrangement in a polyene characteristic of vitamin A more reliably by experiment on animals than by any chemical decomposition reaction or by spectrum analysis measurements. This high specificity is all the more surprising if it is remembered that with regard to most hormones, e.g. the female sexual hormones and the plant growth hormones, we can hardly speak of a constitutional specificity. Not only do substances which are chemically closely related produce there similar physiological results, but it can often happen that compounds of entirely different constitutions show the same effects as the natural products.

This strongly pronounced constitutional specificity of vitamin effects may be connected with the results of the most recent investigations, which re-

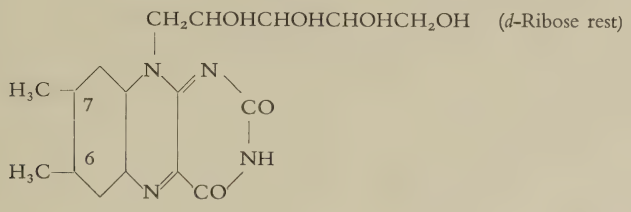
vealed that many vitamins are functional groups of enzymes, the highly specific properties of which have long been known. These close relationships between enzymes and vitamins were first shown in vitamin B_2 or lactoflavin. According to the investigations of Warburg and Theorell the phosphoric acid ester of vitamin B_2 is the functional group of the yellow oxidation enzyme. Today lactoflavin and any other flavin can be obtained synthetically, and hence we were able to investigate at this point to what extent the vitamin effect is bound to a certain constitution.

The process of such a flavin synthesis, one giving the best yields, may be sketched very briefly. Aromatic primary amines are reductively condensed with sugars. These result in compounds of type (*a*). They can then be coupled with diazonium salts to azo-pigments (*b*). By reduction, diamino-derivatives of formula (*c*) are obtained, which combine with alloxan to form the flavin pigment.



By using this and similar methods more than 25 different flavins have been obtained in our laboratory, which differ from one another by the nature of the sugar residues or the substitution in the aromatic ring, amongst them being lactoflavin itself. This experimental material formed the basis

for an assessment of the constitutional specificity of the action of vitamin B_2. As with vitamin A, with lactoflavin the amplitude of variation is extremely narrow. A substitution of the *d*-ribose residue in the lactoflavin



by other sugars practically abolishes the action; only the arabinose compounds still show a weak, stimulating effect. Just as much significance have the two methyl groups in positions 6 and 7. One or the other can indeed still be omitted or substituted by ethyl without the vitamin action being substantially affected. On the other hand, the disappearance of both methyl residues results in complete inactivity. Methyl groups in positions 5 or 8 are unable to restore this again. The action of vitamin B_2 is therefore like that of vitamin A, bound to an exactly circumscribed constitution and configuration.

This specificity makes itself felt not only against higher organisms but also against bacteria. Elvehjem and my former collaborator Strong* were recently able to show that of all the flavins tested, only lactoflavin, 6-methyl-9-(1′,*d*-ribityl)-isoalloxazin,7-methyl-9-(1′,*d*-ribityl)-isoalloxazin, and 6-methyl-7-ethyl-9-(1′,*d*-ribityl)-isoalloxazin can stimulate the growth of lactic acid bacteria, i.e. the same flavins which are effective in experiments on rats. On the other hand, flavins with other sugar residues, and also the arabinose compounds, had no effect at all.

Up to the present only *one* natural vitamin A has been found as a decomposition product of carotene – the axerophtol mentioned above. Nevertheless, various observations (Heilbron, Morton *et al.*) suggest that in certain fish-liver oils, e.g. those of fresh-water fishes, perhaps still other substances occur with a vitamin A action, whose absorption spectra show longer waves than that of axerophtol. There is nothing surprising in this possibility, since we know that a vitamin A effect is peculiar to various synthetic decomposition products of β-carotene *with more than 20 C-atoms*, such as the above-

* The curves on p. 444 were put at my disposal by Dr. Frank M. Strong.

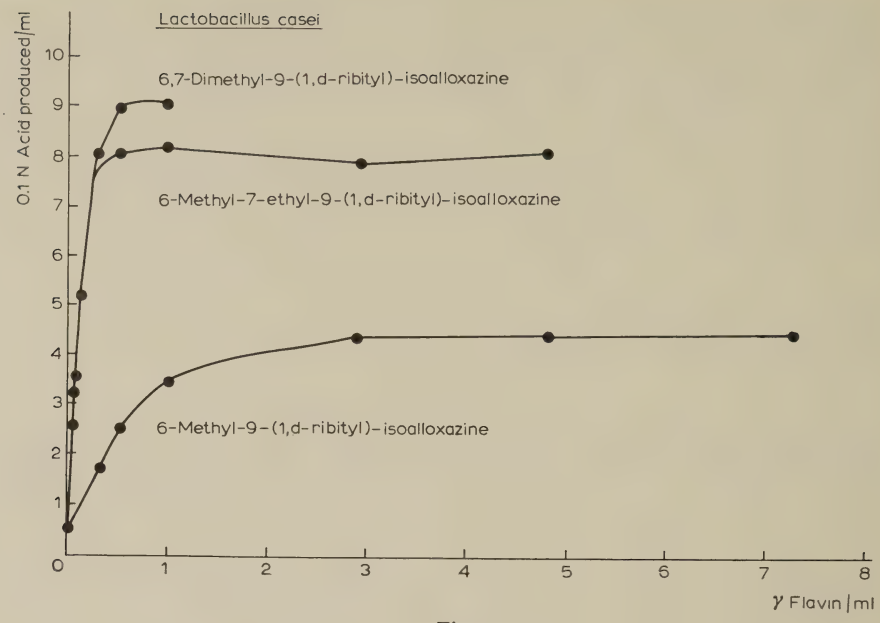

Lactobacillus casei
6,7-Dimethyl-9-(1,d-ribityl)-isoalloxazine
6-Methyl-7-ethyl-9-(1,d-ribityl)-isoalloxazine
6-Methyl-9-(1,d-ribityl)-isoalloxazine
0.1 N Acid produced/ml
γ Flavin/ml
0
1
2
3
4
5
6
7
8
9
10

Fig. 1.

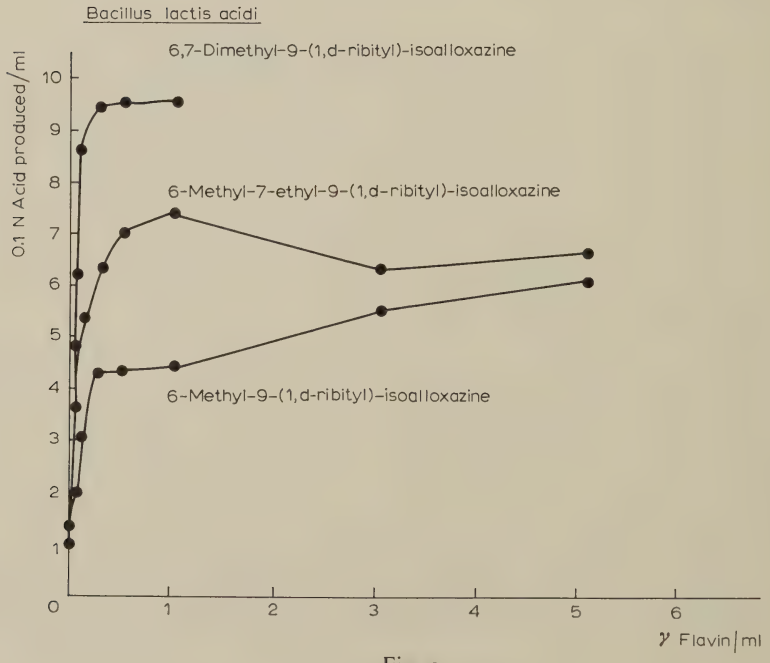

Bacillus lactis acidi
6,7-Dimethyl-9-(1,d-ribityl)-isoalloxazine
6-Methyl-7-ethyl-9-(1,d-ribityl)-isoalloxazine
6-Methyl-9-(1,d-ribityl)-isoalloxazine
0.1 N Acid produced/ml
γ Flavin/ml
0
1
2
3
4
5
6
7
8
9
10

Fig. 2.

mentioned apo-carotenals. The thought occurs that Nature too is treading the path which we have been following in the laboratory of late, i.e. in splitting up carotene not only at the central bonds but also at other double bonds, whereby products must result with a longer chromophore system with more double bonds than the ordinary vitamin A possesses. Such substances will be distinguished by absorption spectra of longer wavelengths. Although vitamin A is one of those vitamins whose physiological effects have long been known – Hopkins (1912), Stepp (1911–1912), McCollum, Simmonds, Becker, and Shipley (1922) – even today we are still very much in the dark with regard to the way it intervenes in the cell phenomenon processes. In the cases of vitamin B_2 (lactoflavin) and B_1 (aneurin), research during the last two years has been more successful in this connection, as the parts played by the first in dehydration reactions and by the second in natural carbohydrate decomposition have been clearly recognized. It is also widely believed today that vitamin A participates in the case of oxidation reduction reactions in the organism. How this intervention happens is, however, still not clearly known.

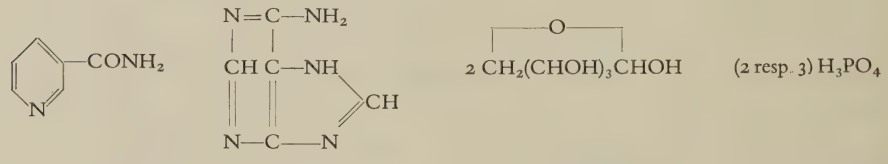
Vitamin A exercises considerable influence on epithelial formation, and many results of an A-avitaminosis are probably the results of the suspension of the effect of the A-factor which promotes the formation of a healthy epithelium. Thus, for instance, A-avitaminosis resulting from injury to the epithelium is connected with lowered resistance to infections; furthermore, in rats it leads to a chronic oestrus (colpokeratose), i.e. the outer layers of the epithelia of the vagina become horny. Modern surgery is making increasing use of the epithelium-promoting effect of vitamin A, by using cod-liver oil preparations, rich in vitamin A, for helping the healing process in wounds; carotene is believed to have a similar favourable effect.

The action of the A-factor on the eyes is remarkably strong; a vitamin deficiency leads to xerophthalmia, the cause of which is sclerotic change, and to night blindness (hemeralopia), a disease which is often encountered, even in these days, among primitive peoples whose nutrition is deficient. It is most remarkable that the eye is one of the organs most rich in vitamins which we know; not only lactoflavin and vitamin C (ascorbic acid), but also vitamin B_1, vitamin K, etc. are present in the eye in considerable quantities. The same applies for the A-factors. Von Euler and Adler have referred to the occurrence of carotenoids in the retina of the eyes of cattle and fish, and G. Wald proved in our laboratory the presence of large quantities of vitamin A (axerophtol) in the retina. According to later in-

vestigations by Wald, vitamin A appears to play an important part in the act of seeing; in the process of exposure to light a pigment, « retinene », combined with a protein and showing a colour reaction with antimony trichloride, is formed from the visual purple. This colour reaction has its absorption maximum at 662–666 mμ. From the retinene, vitamin A is formed (absorption maximum of the antimony trichloride reaction 615 mμ) and finally in the dark the vitamin A is transformed again into visual purple. Eyes kept in the dark contain traces only of vitamin A.

It would seem, therefore, that the chromophore system of the carotenoids is also utilized in the act of seeing, and the animal organism makes varied use of these plants pigments.

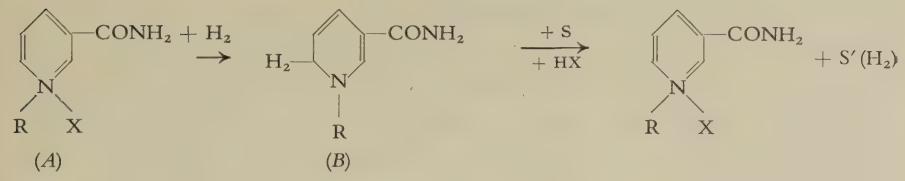
Research into the problems connected with vitamin A took place in a roundabout way; as I have explained before, it began with the chemical treatment and elucidation of the composition of the carotenoids. At that time no one imagined that those investigations would become the foundation for vitamin A research. The same circumstances have applied to various other vitamins. One of the most impressive examples, the last to become known, is the story of nicotinic acid amide. This was recognized by Warburg as a constituent of a coenzyme, codehydrase II, and by von Euler as the building material of the cozymase (codehydrase I), in which it occurs together with adenine, pentose, and phosphoric acid:



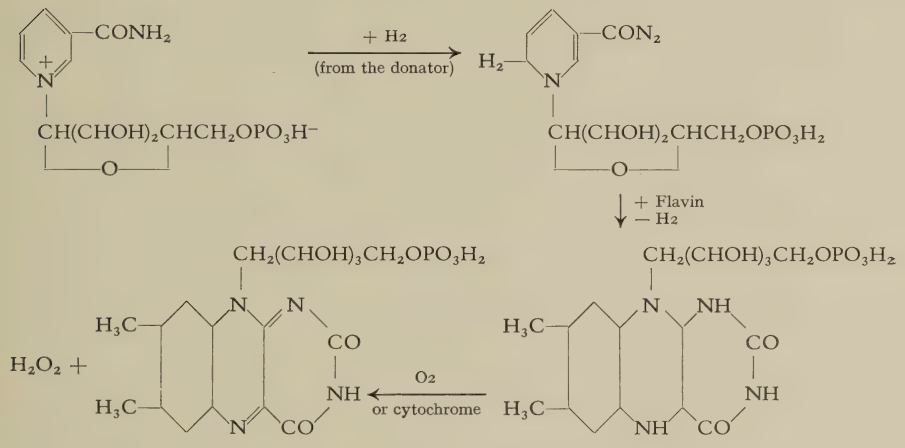
Nicotinic acid amide Adenine Pentose Phosphoric acid

Then, together with O. Warburg, we were jointly able to show that the hydrogen-transferring role, i.e. the central significance, devolves precisely upon this constituent of the two codehydrases in the oxidation-reduction processes.

A hydrogen transference was found to be possible only through such nicotinic acid amide derivatives in which the pyridine nitrogen has a quarternary character. Such compounds (Formula A) are transformed by assimilating the hydrogen split from the substrate into *ortho*-dihydro derivatives (Formula B), which then pass on the hydrogen to other compounds (S):



In the two codehydrases it is the sugar residue, the pentose residue, which stands in quaternary bond at the pyridine nitrogen of the nicotinic acidamide; the dehydration of the resultant dihydronicotinic acid compound is effected through the chromophore system of the yellow enzyme, i.e. through lactoflavin (vitamin B_2). The entire dehydration process is represented by the following structural formulae:



As a result of these investigations nicotinic acid amide suddenly became of general interest. It was tried as a remedy in the most varied kinds of diseases, and in doing this Elvehjem and his co-workers discovered that it is the cure for the «black tongue» disease in dogs, on which experiments had been carried out for decades. We are therefore dealing in this instance with a newly discovered supplementary factor in nutrition, a new vitamin.

It has often been said that it is only the first discovery which is difficult and that the ensuing discoveries are usually only the continuations of the first. Perhaps vitamins and carotenoids offer examples of this.

In a lecture which I gave in 1932 I remarked: «The chemistry of the vitamins has made great progress in the last few years; it has overtaken the

chemistry of the hormones and left that of the enzymes far behind. Soon we shall be so far advanced that all kinds of positive statements can be made about the chemical nature of the different vitamins. Then the chemist will be able to hand back the vitamin problem to the physiologist, so that the latter may establish in what way these substances develop their effect in the organism. Once physiology has solved this problem, it will have become enriched by one of its greatest findings.»

This prophecy has been fulfilled to a large extent within the short space of five years. The chemical side of the vitamin problem is solved in its essential points; relationships to enzymes were found. It is the task of physiology today to explain the intervention of these agents in the cell processes. As this is, however, a matter of chemical processes, these will in the end probably have to be elucidated by the chemist once again.

Biography

Paul Karrer was born in Moscow on April 21, 1889. His parents, Paul Karrer and Julie Lerch, were Swiss nationals and in 1892 the family returned to Switzerland where he received his early education at Wildegg and at the grammar school in Lenzburg, Aarau, where he matriculated in 1908. He studied chemistry at Zurich University under Professor Alfred Werner and after gaining his Ph.D. in 1911, he spent a further year as assistant in the Chemical Institute. In 1912 he took a post as chemist with Paul Ehrlich at the Georg Speyer Haus, Frankfurt-am-Main; he left Frankfurt six years later on his election as reader at Zurich University. In 1919 he became Professor of Chemistry and Director of the Chemical Institute.

His early researches involved the preparation and investigation into the properties of complex metal compounds but his most important work has concerned plant pigments, particularly the yellow carotenoids. He was responsible for elucidating the chemical structure of the carotenoids and he also showed that some of these substances are transformed in the animal body into vitamin A. His work in this field led, in 1930, to the establishment of the correct constitutional formula for β-carotene, the chief precursor of vitamin A; this, the first time that the structure of a vitamin or provitamin had been established, in turn led to the clarification of the structure of vitamin A itself. Later, he confirmed the structure ascribed to ascorbic acid (vitamin C) by Albert von Szent-Györgyi and he extended his researches into the vitamin B_2 and E fields. His important contributions to the chemistry of the flavins led to identification of lactoflavin as part of the complex originally thought to be vitamin B_2.

Professor Karrer has published over 1,000 scientific papers in the various fields of organic chemistry, especially concerning vitamins A, B_2, C, E and K, co-enzymes, carotenoids and other plant pigments, curare and other alkaloids, amino acids, carbohydrates and organo-arsenic compounds. His *Lehrbuch der Organischen Chemie* (1930) has passed through 13 editions and has been translated in full into English, Italian, Spanish, French, Polish and Japanese. His monograph on carotenoids (1948) has also been translated into English.

Karrer was President of the 14th International Congress on Pure and Applied Chemistry (Zurich, 1955). He has received honorary doctorate degrees from universities in Europe and America; they include Dr. med. Basle, Breslau, Lausanne and Zurich; Ph.D. Lyons, Paris, Sofia, London, Turin, Brussels and Rio de Janeiro; and Dr. Pharm. Madrid and Strasbourg. He has been awarded the Marcel Benoist Prize and the Cannizzaro Prize and he is a full member or honorary, corresponding or associate member of numerous chemical and biochemical societies throughout the world. These include the Académie des Sciences (Paris); the Royal Society (London); National Academy of Science (Washington); Royal Academy of Sciences (Stockholm); the National Academy (Rome); Royal Academy of Belgium; the Indian Academy of Science; the Royal Netherlands Academy of Sciences, and the Chemical Societies of Britain, France, Germany, Belgium, India and Austria.

Karrer married Helena Froelich in 1914. They have two sons.

Chemistry 1938

RICHARD KUHN

«*for his work on carotenoids and vitamins*»

Chemistry 1938

The following account of Kuhn's work has been made

When Richard Kuhn in 1926 took over the Chair for General and Analytical Chemistry at the Federal Institute of Technology Zurich he set in motion a comprehensive series of investigations into the so-called conjugated double bonds which make up the essential arrangement of the atoms of the polyenes.

The group of the diphenylpolyenes had at this time aroused especial interest because the presence in the carotenoid Crocetin of a chain of double bonds had been successfully demonstrated. Kuhn's sixth report on conjugated double bonds already contains structure determinations of polyene dyes from vegetable materials. With his syntheses of over 300 new materials belonging to this group Kuhn has by no means sought merely to liberate new substances. In this work he was much more concerned to clarify the general relationships between the chemical structure of these unsaturated substances and their optical, dielectric, and magnetic properties. The results which he has obtained in this respect form the starting-point for new lines of development in organic chemistry.

Kuhn's work on polyenes led him straight into the chemistry of the carotenoids. In 1930 Karrer clarified the constitution of carotene. The elementary composition of carotene, $C_{40}H_{56}$, had previously been ascertained by Willstätter. In 1931, R. Kuhn (at that time already Professor at Heidelberg), Karrer in Zurich, and Rosenheim in London discovered simultaneously and independently of each other the fact that the carotene in carrots consists of two separate components: one of these, β-carotene, rotates the plane of polarized light to the right, while the other, α-carotene is optically inactive. In 1933 Kuhn discovered a third carotene isomer which was called γ-carotene.

The great physiological and biological significance of carotene lies in the fact that it is hydrolysed in the liver of certain animals so that from one molecule of β-carotene or from two molecules of α-carotene two molecules of Vitamin A, Axerophtol, are formed. This substance is necessary for growth in higher animals and especially for maintaining the normal condition of the mucous membranes.

With several collaborators Kuhn carried out a large number of investigations into the occurrence of carotenoids in the animal and vegetable kingdoms. Among his most important results, his discoveries of the following carotenoids and their structure determination should be mentioned:

Physalien from berries of species of *Physalis*, Helenien, Flavoxanthin, isolated from species of *Ranunculus*, Violaxanthin from *Viola tricolor*, unstable Crocetin from saffron, Taraxanthin, Cryptoxanthin from *Zea Mays* Rubixanthin.

Kuhn also had an important share in establishing the composition of Rodoxanthin and Astaxanthin as well as in discovering the connection of this latter carotenoid with the chromoproteids of the Crustaceans.

Of great interest also are the many contributions Kuhn and his school have made to the perfection of the chromatographic method which is one of the most important aids to the isolation and synthesis of the different representatives of the carotenoid group.

Kuhn's second great field of activity concerns the clarification of the Vitamin B complex. Kuhn has the great merit, together with v. Szent-György and Wagner-Jauregg, of having been the first to isolate the extraordinarily important substance Vitamin B_2 (Lactoflavin or Riboflavin). He has made very important contributions to the elucidation of the chemistry of this substance.

From 5,300 litres skim milk Kuhn and his collaborators succeeded in liberating about 1 g of a pure yellow substance, Lactoflavin, whose composition was found to be $C_{17}H_{20}O_6N_4$. A breakdown product of the Lactoflavin, which was called Lumiflavin, could be identified with a substance previously prepared from the yellow ferment occurring in yeast. By drawing up a structural formula for Lumiflavin later confirmed in various ways, Kuhn furnished a key to the chemical clarification of Lactoflavin. He himself demonstrated the Lumiflavin formula, which had been found by analytical methods, by a synthesis–namely through the condensation of an *o*-diaminobenzene derivative with Alloxan.

At the beginning of 1939 Kuhn made his second significant discovery in relation to the Vitamin B complex. Together with Wendt, Andersag, and Westphal, he succeeded in isolating that component of the Vitamin B complex which is designated Vitamin B_6, the antidermatitis vitamin, and in a remarkably short time he was able to establish its chemical composition and structure (*Ber.*, 71 (1938) 1534; 72 (1939) 309). The substance which Kuhn

thus elucidated, which he called *Adermin*, proved to be 2-methyl-3-hydroxy-4,5-dihydroxymethylpyridine*.

* Professor Richard Kuhn was awarded the Nobel Prize in Chemistry for 1938, for his work on carotenoids and vitamins. Owing to political conditions at the time, Professor Kuhn was prevented from accepting the prize. In 1949 he received the gold medal and the diploma.

No Lecture was delivered by Professor R. Kuhn

Biography

Richard Kuhn was born in Vienna on December 3, 1900. His father, Richard Clemens Kuhn, was an engineer and «Hofrat»; his mother, Angelika Rodler, was a teacher in elementary schools. He was educated at the «Gymnasium» (grammar school). He studied chemistry at Vienna University and later at Munich under R. Willstätter. He obtained his degree (D. Ph.) in 1922 following his thesis *Über Spezifität der Enzyme* (On the specificity of enzymes).

In 1925 Munich University invited him to lecture on chemistry. Kuhn accepted an invitation by the Eidgenössische Technische Hochschule in Zurich, where he held the post of Professor for General and Analytical Chemistry from 1926 until 1929. He then became Principal of the Institute for Chemistry at the newly founded Kaiser-Wilhelm-Institut (since 1950, Max Planck Institut) for Medical Research in Heidelberg; in 1937 he also took over the administration of this Institute, in succession to L. von Krehl. Besides these duties he also filled the post of Professor of Biochemistry at the University of Heidelberg. For one year he was at the University of Pennsylvania, Philadelphia, as a Visiting Research Professor for Physiological Chemistry.

Kuhn investigated theoretical problems of organic chemistry (stereochemistry of aliphatic and aromatic compounds; syntheses of polyenes and cumulenes; constitution and colour; the acidity of hydrocarbons), as well as extensive fields in biochemistry (carotenoids; flavins; vitamins and enzymes).

For a period of twenty years Kuhn investigated compounds containing double bonds which proved to be of great interest in connection with the study of the chemical nature of the carotenoids. He discovered eight new types of these and was able to analyse their constitution. He also carried out important work on vitamin B_2 and the antidermatitis vitamin B_6. For his work in this important field Kuhn was awarded the Nobel Prize for Chemistry in 1938.

Kuhn received numerous other honours and awards in recognition of his

work; he was awarded honorary degrees of the Technische Hochschule in Munich (1960), the University of Vienna (1960), the University of St. Maria, Brazil (1961). An impressive number of medals and prizes have been presented to him, as well as orders and the highest possible honours, in many countries. Kuhn is also a member of many scientific academies, societies and organizations in all parts of the world. He is the President of the Society of German Chemists, Vice-President of the Max Planck Society and Editor of *Liebigs Annalen der Chemie*. He belongs to the Board of the « Badische Anilin- und Soda-Fabrik ».

It may be mentioned that for a period of eight years (1910-1918) Richard Kuhn was a schoolmate of Wolfgang Pauli who was awarded the Nobel Prize in Physics for 1945.

Richard Kuhn married Daisy Hartmann in 1928 and has two sons and four daughters.

Chemistry 1939

ADOLF FRIEDRICH JOHANN BUTENANDT

«for his work on sex hormones»

LEOPOLD STEPHEN RUŽIČKA

«for his work on polymethylenes and higher terpenes»

Chemistry 1939

The following account of Butenandt's work has been made

As recently as twelve years ago, very little was known about the nature of the sex hormones. As regards the oestrogenic, or follicle, hormone it was established that extracts from certain organs, e.g. the ovaries and placenta, bring about the characteristic oestrus phenomena in castrated female rats. Only a few observations were available concerning the stability and solubility of their active principles. Further development in the chemistry of the oestrogenic hormones could not take place until the purely biological discoveries by Allen and Doisy in 1923 and by Aschheim and Zondek in 1927 had been made.

Butenandt made the first big step forward in clarifying the chemistry of the follicle hormone in 1929 in Göttingen, simultaneously with Doisy in the United States. Both workers succeeded in isolating from the urine of pregnant women a substance in crystalline form having oestrogenic effects. Butenandt named this substance folliculine, a designation which was later changed to *oestrone*. He established that its empirical formula was $C_{18}H_{22}O_2$, and that it was an oxyketone.

Shortly after the discovery of oestrone, Marrian in London (1930) isolated from the urine of pregnant women a new hormone which he called *oestriol*. Butenandt confirmed Marrian's discovery and explained the relationship between the new substance and oestrone. The relation between sterols and oestrogenic substances which had been assumed on crystallographical grounds became probable from the chemical point of view only after Butenandt and Marrian had shown, independently of one another, that only three benzoide double bonds enter into the ring system of these substances.

In 1932, Butenandt was able, from observations made in spectral analysis, and especially on the basis of the then established correct formula of cholesterol to draw up the formulae of the chemical structure of oestrone and oestriol. But there remained the important task of proving the chemical structure of the ring system as assumed by Butenandt. By breaking down the oestriol molecule stage by stage Butenandt proved that *both œstrogenic hormones contained a phenanthrene core*. At the same time he was able to obtain the

same dimethyl phenanthrene from etiobilianic acid, a transformation product of cholic acid. He had thus confirmed the close relationship existing between the follicle hormones on the one hand and the bile acids and sterols on the other.

The second important ovarian hormone, the corpus luteum hormone, was by various workers obtained in crystalline form from corpus luteum in 1931 and 1932. In 1934, Butenandt and Westphal succeeded in producing this hormone, which was given the name progesterone, in a chemically pure form. They also demonstrated its close relationship with pregnanediol, a physiologically inactive dihydric alcohol which Butenandt and Marrian had found independently of one another in the urine of pregnant women. In the autumn of 1934, Butenandt succeeded in converting pregnanediol into progesterone. The synthesis of this important pregnancy hormone from cholesterol was carried out by Butenandt in a simple way in 1939.

The merit of the chemical exploration of the testicular, or androgenic, hormones falls to Butenandt and Ružička in common. Butenandt was the first to tackle this problem, and it was only possible to work on it after biological research had found a quantitative test for the determination of these substances – the so-called capon comb test.

Butenandt started with male urine, or alternatively its chloroform extract – approximately 0.8 per thousand dissolved in chloroform. In the process of purification it proved that the male hormone behaved in many respects like oestrone; when he realized this, it made Butenandt's work considerably easier.

When the purification had been successfully accomplished, there presented for the first time a crystalline substance with the physiological properties of a male sex hormone.

Butenandt gave this substance the name androsterone and defined its composition as $C_{19}H_{30}O_2$. It differs from oestrone only in the additional content of 1 methyl group and 5 hydrogen atoms. Butenandt drew up the full constitutional formula in 1934 on the basis of the formula of cholesterol.

Androsterone had been synthesized from epi-cholestanol by Ružička, but it soon proved to be not identical with the genuine male hormone from the testicles. For this reason it made a great stir when in 1935 Laqueur and his collaborators isolated from testicular extract a highly active hormone– testosterone.

The close relationship of testosterone to androsterone made it comparatively easy to clarify its chemical composition, and still in the same year 1935

Ružička and Butenandt were able, in the same way but independently of each other, to obtain testosterone from *trans*-dehydro-androsterone.

Butenandt, Ružička and others then produced from sterols various new substances which, when tested as male sex hormones, were found to be active in varying degrees.*

* Professor Adolf Butenandt was awarded half of the Nobel Prize in Chemistry for 1939, for his work on sex hormones. Owing to political conditions at the time, Professor Butenandt was prevented from accepting the prize. In 1949 he received the gold medal and the diploma.

No Lecture was delivered by Professor A. Butenandt

Biography

Adolf Frederick Johann Butenandt was born on March 24, 1903 at Bremerhaven-Wesermünde. The son of a business man Otto Butenandt of Hamburg, he went to school at Bremerhaven and studied chemistry at the Universities of Marburg and Göttingen. In 1927 he graduated at the University of Göttingen, where he had studied under Adolf Windaus.

From 1927 until 1930 he was Scientific Assistant at the Institute of Chemistry, Göttingen, and from 1931 until 1933 he was Privatdozent in the Department of Biological Chemistry at the University of Göttingen and acting Head of the laboratories for organic and inorganic chemistry. He then became Professor Ordinarius and Director of the Institute for Organic Chemistry at the Institute of Technology at Danzig, a post which he held until 1936.

From 1936 until 1960 he was Professor in the University of Berlin and Director of the Max Planck Institute for Biochemistry, Berlin-Dahlem, which later moved to Tübingen and then to Munich. From 1945 until 1956 he was Professor of Physiological Chemistry at Tübingen and in 1956 he became Professor of Physiological Chemistry in the University of Munich. From 1956 until 1960 he was Director of the Institute of Physiological Chemistry in the University of Munich.

Since 1960 he has been President of the Max Planck Society at Munich.

Butenandt's name will always be associated with his work on sex hormones, for which he was awarded, jointly with Leopold Ruzicka, the Nobel Prize for Chemistry for 1939. In 1929 he isolated oestrone in pure, crystalline form, almost at the same time that E. A. Doisy did this in America. In 1931 he isolated androsterone in pure, crystalline form. From androsterone he as well as Ružička, independently of each other, obtained testosterone in 1939, a compound which had been obtained from the testes in 1935 by Ernst Laqueur. Progesterone was isolated by Butenandt from the corpus luteum in 1934.

In addition to these researches, Butenandt carried out much investigation of the interrelationships of the sex hormones and on the possible carcino-

genic properties of some of them. His work on the sex hormones was largely responsible for the production of cortisone on a large scale.

A great number of honours and distinctions was bestowed upon him. He was awarded several medals and prizes from Germany, France, Sweden and England, he received the Grand Cross for Federal Services with Star (1959), he holds six honorary doctorates (Munich, Graz, Leeds, Madrid and two from Tübingen) and is Freeman of the City of Bremerhaven. He is corresponding member of the Academy of Sciences at Göttingen, honorary life member of the New York Academy of Sciences, and honorary member of the Japanese Biochemical Society, the Deutsche Akademie der Naturforscher Leopoldina, Halle, and the Austrian Academy of Sciences.

He married Erika Ziegner in 1931; they have seven children and live at Munich-Obermenzing.

Chemistry 1939

The following account of Ružička's work has been made

The higher terpenoids or polyterpenes, which occur in great variety in the vegetable kingdom, were originally the main subject of Ružička's investigations, and the extremely difficult determination of their structure has been made possible through his exceptional experimental skill. The pioneering work of Ružička and his co-workers has led to thorough investigations of a very large number of important polyterpenes.

When studying the natural odorants occurring in musk and civet, muscone and civetone, little known until then, Ružička obtained fundamentally new and surprising results during the years 1924–1926. He discovered that the molecule of muscone as well as that of civetone contains one single ring of carbon atoms, the number of which was considerably larger than that in all hitherto known cyclic molecules, larger even than had been considered possible. During his investigations of these odorants he synthesized many kindred macrocyclic compounds, and drew attention to the plant-physiologically remarkable fact that these could be prepared from natural fatty acids.

Many interesting relationships exist between the polyterpenes studied by Ružička and a series of physiologically and medicinally important groups of compounds, viz. the bile acids, the sterols and the sex hormones. Among the many interesting results obtained by Ružička and his collaborators with sex hormones, the preparation of compounds with the same action as male sex hormones is of signal importance. It is his merit that by establishing preparative methods for androsterone and testosterone the technical synthesis of these two hormones has been made possible.

Moreover, the numerous new related compounds prepared by Ružička have contributed fundamentally to our knowledge of the physiologically so very important sex hormones, thus creating a sound basis for future investigations*.

* Professor L. Ružička was awarded half of the Nobel Prize in Chemistry for 1939, for his work on polymethylenes and higher terpenes. Owing to the war conditions Professor Ružička attended the ceremonies later in 1945.

At a special ceremony in Zurich the prize was handed over to Professor Ružička by the Swedish ambassador Baron H. G. Beck-Friis on January 16, 1940, after a speech ending with the following words:

Professor Ružička. On behalf of the Nobel Foundation and the Royal Swedish Academy of Sciences I convey to you the most cordial congratulations – to which I may be permitted to add my own – and at the same time express my hope that you will be able to extend your research successfully to ever-increasing fields in the service of mankind.

With this hope I have the honour to present you with the Certificate of the Nobel Prize for Chemistry for the year 1939 and with the Nobel Medal.

Leopold Ružička

Multimembered rings, higher terpene compounds and male sex hormones

Nobel Lecture, December 12, 1945

This lecture should have been delivered in December 1939*, but owing to a postponement of 6 years forced by the intervention of war, I have been able to use some results obtained in the meantime to round off the overall picture. Consequently I can now report on the results of 25 years of laboratory work in two fields of the chemistry of alicyclic compounds: multimembered rings and higher terpene compounds (polyterpenes), to which the third group named in the title, the male sex hormones, is closely related.

Alicyclic compounds scarcely differ in their chemical properties from their aliphatic analogues. Many investigations, especially during the past twenty-five years, have shown, however, that in spite of this close chemical similarity aliphatic compounds and their alicyclic analogues can exhibit entirely different physiological properties. We see that certain well-defined physiological properties may appear or disappear in the transition from an aliphatic to an alicyclic compound or vice versa. As a result of the accumulation of such observations, alicyclic compounds to which only scant biochemical importance was attached as little as 20–25 years ago, have now advanced to the forefront of interest.

Multimembered rings

After Kekulé, in 1865, first introduced the carbon ring into structural chemistry in his formula for benzene, the 6-membered ring maintained its unique position in the taxonomy of organic chemistry for several decades. Indeed, a heterocyclic 5-membered ring containing nitrogen became known in 1870 as a result of Adolf von Baeyer's work on indigo; but this did not imme-

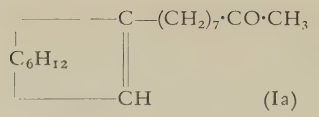
* Data available at that time formed the subject of a number of lectures which I delivered between December 1939 and April 1940 in Zurich, Zagreb, Utrecht, Amsterdam, Delft, Liège, Brussels and Paris. This material was published in Croat in the Zagreb medical journal *Liječnički vjesnik*, Vol. 62, July 1940.

diately stimulate attempts to prepare small carbocyclic rings. In the first Pedler Lecture delivered before the Chemical Society in London in 1929, W. H. Perkin Jr.[1] described « the early history of the synthesis of closed carbon chains ». He dealt not only with the reactions which led to the synthesis of small carbon rings during the period 1881–1883, but also with the pessimistic views of the leading chemists of that time regarding the possible existence of carbocycles other than the 5- and 6-membered rings. Adolf von Baeyer, Emil Fischer, and Viktor Meyer advised Perkin not to waste his time on attempts to prepare such compounds, which could « hardly be capable of existence ».

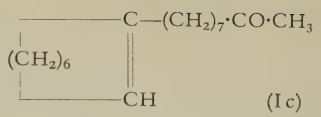
The systematic researches of Perkin and the roughly contemporary work of other authors – special mention should be made of Markovnikov[2] and Freund[3] – led, in the course of a few years, to the establishment of the chemistry of small, i.e. 3- to 5-membered carbon rings. The 7- and the 8-membered ring was also subsequently prepared by various methods, whilst attempts by Zelinsky and Willstätter to prepare the 9-membered ring were unsuccessful, and accordingly the prejudice regarding the impossibility of synthesizing carbocycles with more than 8 members in a ring continued. The unsuccessful attempts to expand the cyclic system beyond the 8-membered ring led to the view that von Bayer's strain theory, which was based on the work of Perkin and others interpreting the ease of formation and the properties of 3- to 6-membered rings, is also applicable to ring systems containing more than six members. According to this theory, the inaccessibility of larger rings is due to the strain resulting from the arrangement of all the ring members in one plane, and the consequent deviation of the valency angles from their normal position.

Sachse[4] had already pointed out that strain free models are possible for rings containing 6 and more members, provided that Baeyer's assumption of a planar structure is disregarded. Böeseken[5] showed experimentally in 1922–1924, that a planar structure is improbable for 6- and 7-membered rings, and in 1926 Hückel[6] proved chemically – as far as such a proof can be achieved by chemical means – that the 6-membered ring is not planar, at least in the case of decalin.

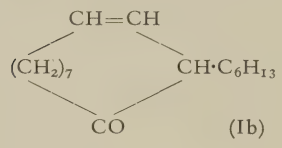
At that time, from 1922 on, I was engaged in the elucidation of the constitution of the natural musk perfumes, civetone $C_{17}H_{30}O$, and muscone $C_{16}H_{30}O$, and was able to show conclusively that civetone contains a 17-membered, and muscone a 15-membered carbon ring. In the original experiments, which were carried out on civetone[7], I was hindered less by the caprices of the substance itself than by the general prejudice, shared by my-



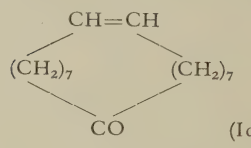
(Ia)



(Ic)



(Ib)



(Id)

Civetone

HOOC-$(CH_2)x$-COOH (II)

$x=7$, Azelaic acid $x=5$, Pimelic acid
$x=6$, Suberic acid $x=4$, Adipic acid

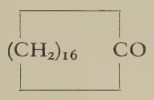
self, against the probability of the existence of a 15- and a 17-membered ring.

Degradation of civetone with a large quantity of potassium permanganate or with ozone, followed by further oxidation of the degradation products with hypobromite, yielded a mixture of normal dicarboxylic acids (general formula II), which could be readily separated by fractional distillation of the esters. The pure acidic products were characterized as azelaic, suberic, pimelic, adipic and succinic acids.

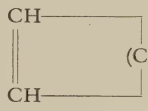
Formula (Ia) was therefore considered as a possible partial formula for civetone*, on the assumption that it contained a substituted 6-membered ring. An analogous formula with the grouping $(CH_2)_7$ in the ring seemed less likely since this represents a 9-membered ring. Formulae of the type (Ib) involving a ring with at least 11 members in which both the keto-group and the double bond lie in the ring, were even less likely. Furthermore, oxidation of civetone with a small amount of potassium permanganate or with ozone yielded a keto dicarboxylic acid $C_{16}H_{28}O_5$ or $C_{17}H_{30}O_5$, which on further degradation with potassium permanganate and alkaline hypobromite gave only some of the above-mentioned normal dicarboxylic acids (II). Since there was no indication of the formation of degradation products other than the normal dicarboxylic acids, a normal chain structure (Ic containing an 8-membered ring) had also to be considered for the portion of the carbon skeleton denoted by C_6H_{12} in formula (Ia).

* In the original publications, no mention was made of the fact that, in the course of the work, the supposed formulation for civetone did not progress in one step from the 6-membered to the 17-membered ring. I believe, however, that the subsequent description of some considerations involved in the elucidation of the constitution of civetone may be of some interest.

Finally, when we found that both the hydrogenation product of civetone, i.e. dihydrocivetone (III), and the unsaturated hydrocarbon (IV) obtained by Wolff-Kishner reduction of civetone give the same dicarboxylic acid $C_{17}H_{32}O_4$, were we forced to discard formulae of the type (Ia)–(Ic) and to consider the completely symmetrical formula Id for civetone. The formulation of the dicarboxylic acid $C_{17}H_{32}O_4$ as heptadecane-1,17-dioic acid (V), as suggested by these considerations, was irrefutably confirmed by comparison with the synthesized product[8]. The carefully purified keto dicarboxylic acid $C_{17}H_{30}O_5$ was identified as 9-ketoheptadecane-1, 17-dioic acid (VI), since it could be synthesized by heating a monoester of azelaic acid with iron. A further confirmation of the presence of the 17-membered ring in civetone is provided by the synthesis of dihydrocivetone by cyclisation of the synthetic octadecane-1, 18-dioic acid (VII).



(III)



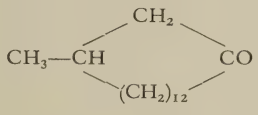
(IV)

$$HOOC—(CH_2)_{15}—COOH \qquad (V)$$

$$HOOC—(CH_2)_7—CO—(CH_2)_7—COOH \qquad (VI)$$

$$HOOC—(CH_2)_{16}—COOH \qquad (VII)$$

The fact that dihydrocivetone still possesses practically the same odour as civetone suggested that in the case of muscone ($C_{16}H_{30}O$), which does not contain a double bond, the musk odour is also due to the presence of a multimembered ring. Since muscone is optically active, it could contain at most a 15-membered ring with a methyl side-chain, if the above assumption is valid. This conclusion was found to be correct, and it was shown that muscone is the optically active β-methylcyclopentadecanone (VIII).

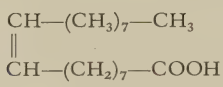


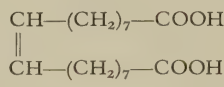
(VIII)

Muscone

Civetone (Id) and muscone (VIII) seemed, both as natural products and in the system of organic chemistry to break the old empirical rule « Natura non fecit saltus ». Speculations on the probable mechanism of the biochemical formation of these two ketones lead to a plausible explanation for their unusual

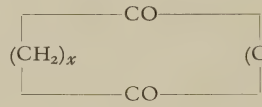
structure. Civetone could perhaps originate in the civet cat by ω-oxidation of oleic acid (IX), followed by cyclization of the unsaturated dicarboxylic acid (X). Muscone could also be a product of fatty acid metabolism. Thus the constitution of the two animal musk perfumes may perhaps be the result of cyclization reactions at the end of the long chain of higher fatty acids[9].


(IX)


(X)

The 15- and 17-membered rings were unable to maintain for long their initially lonely position in the system of organic chemistry. The well-known method of preparing cyclic ketones by the dry distillation of Ca-salts of dicarboxylic acids could be used after slight modification, to prepare the entire homologous series of cyclic ketones, starting with the 9-membered ring and extending beyond the 30-membered ring. Systematic experiments showed that salts of dicarboxylic acids with metals of groups 3 and 4 of the periodic system, and in particular with cerium or thorium, are suitable for this purpose[10]. In all cases examined, it was possible to isolate the expected cyclic ketone. Whereas the yield falls continuously from the 6-membered ring (approx. 70%) to the 10-membered ring (approx. 0.1%), it begins to rise once more with the 11-membered ring, and reaches a maximum (about 5%) with the 16-membered ring, after which it again falls to a few per cent. The constitutions of all the cyclic ketones prepared were determined by oxidation to the normal dicarboxylic acids with the same number of carbon atoms.

The accessibility of some ring systems is facilitated by the fact that the formation of the anticipated monoketones in the cyclisation is accompanied by the formation of the cyclic diketones (XI) with molecules twice as large. This method gave the 34-membered diketone, formed together with dihydrocivetone, as the largest carbocyclic system. This could be reduced to the 34-membered monoketone and the corresponding hydrocarbon.


(XI)

The derivatives of the 30-membered ring in particular became relatively readily accessible for investigation, since cyclotriacontane-1,16-dione is obtained as a by-product in the technical preparation of cyclopentadecanone («Exaltone»), which is used as a synthetic musk perfume.

Table 1.

Number of units in the polymethylene	2	3	4	5	6–8	15	30
Heat of combustion in kcal per CH_2-group	170	168	165	159	158	157	156

The low yields of the higher ketones are not due to any chemical instability comparable to that of the 3- to 4-membered ring compounds, since they can be heated to 400° or with concentrated hydrochloric acid in a sealed tube, to 150° without undergoing ring cleavage or isomerisation. The heats of combustion of a number of multimembered ketones and hydrocarbons were determined as a physical evaluation of their stabilities. Table 1 shows the heats of combustion per CH_2-group in the 8-, 15-, 17- and 30-membered polymethylenes[11], as well as the known values for ethylene and the 3- to 8-membered polymethylenes. It can be clearly seen that, as the number of members of the ring increases beyond six, the heat of combustion does not increase; on the contrary it exhibits a slight but definite decrease, and with the 30-membered ring, reaches the value of about 156 kcal characteristic for an aliphatic CH_2 group.

The spatial molecular structures of a number of multimembered ring compounds were studied by X-ray methods[12]. The measurements on the higher-molecular polymethylenes clearly show an approximately linear increase in the longest period with the number of carbon atoms in the molecule. Thus for instance, from the difference in length between the 24-membered and the 28-membered cyclic diketones it was possible to calculate the value of 1.25 Å for the length of a chain unit and a value of $18.7 \cdot 10^{-16}$ cm² for the half cross-section of the molecule, i.e. the cross section of the single CH_2-chain. These values closely agree with the corresponding figures for normal paraffin hydrocarbons. Thus the structure of the multimembered ring compounds appears to consist essentially of two parallel chains of CH_2 groups closed at both ends. For purposes of comparison, we show here photographs of the 6-, 10-, and 15-membered hydrocarbons (cyclohexane, cyclodecane and cyclopentadecane) as represented by the well-known Stuart models for carbon and hydrogen (cf. Figs. 1–3). In the case of the 6-membered ring, the inner portion of the molecule consists entirely of carbon atoms, whilst the hydrogen atoms form an outer shell. As the number of ring members increases, some of the hydrogen atoms come to lie inside the ring, and the two parallel chains, corresponding to the model of normal paraffin chains, are clearly visible in the 15-membered ring, and even more so in the higher homologues.

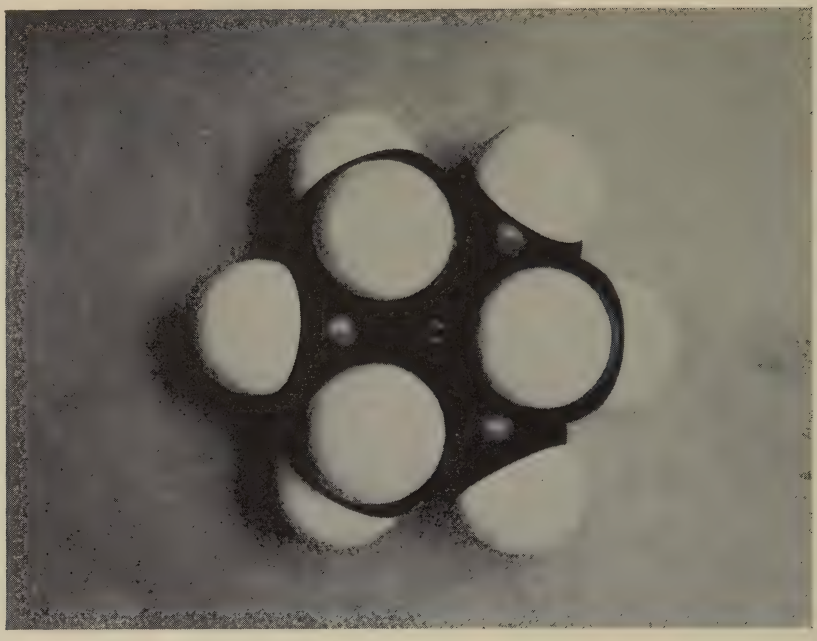


Fig. 1. Cyclohexane.

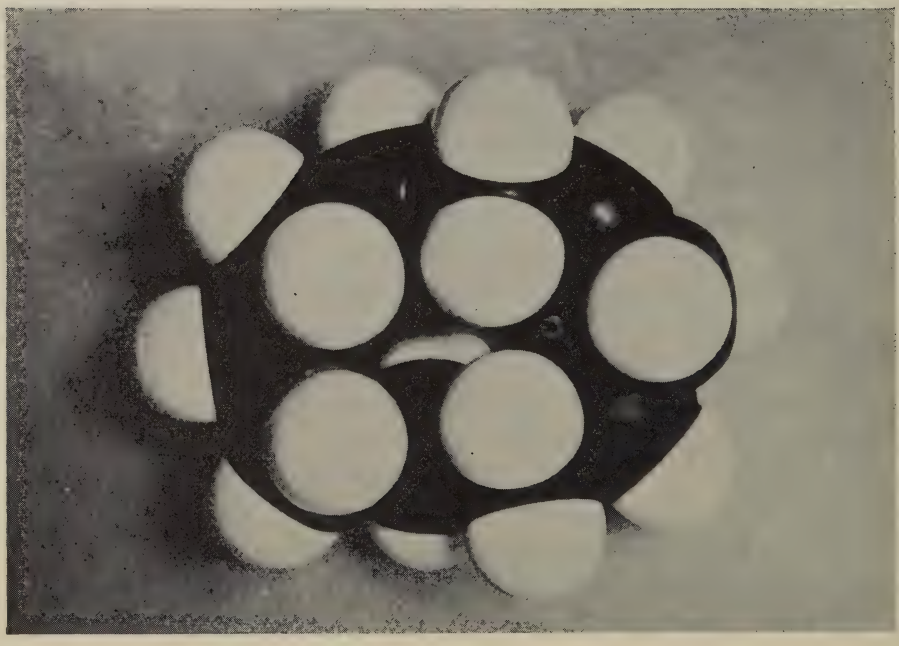


Fig. 2. Cyclodecane.

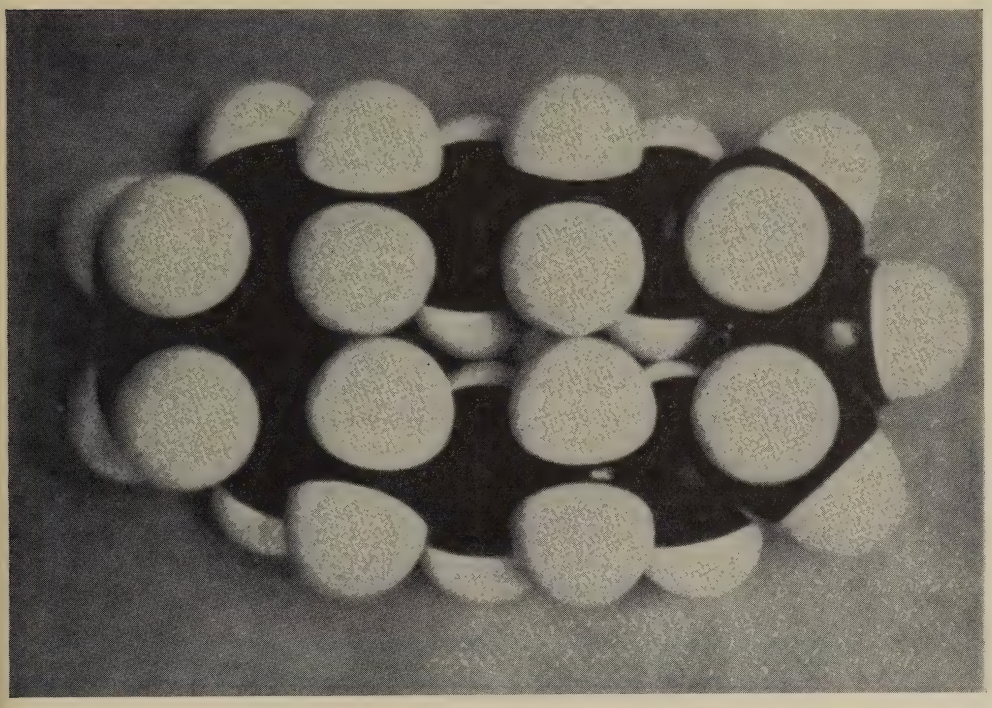


Fig. 3. Cyclopentadecane.

Of the other physical properties of multimembered rings, we shall mention only briefly the melting point and the specific gravity. For purposes of comparison, Fig. 4 shows the melting point curves of the homologous series of the normal paraffin hydrocarbons and of the cycloparaffins (polymethylenes). Whereas the melting point curve of the normal paraffins exhibits the familiar regular zig-zag shape, that of the cyclic hydrocarbons is extremely irregular up to the 15-membered ring. Beginning with the 16-membered ring, the melting point curve of the cyclic paraffins also becomes regular and approximately parallel to that of the normal paraffins. This « normalisation » thus takes place in the cyclic series at approximately the same number of carbon atoms in the molecule as that at which the initially zig-zag curve of the aliphatic series assumes an approximately linear course.

The orthobaric density curves* of the normal paraffins and the cyclic hydrocarbons also exhibit characteristic differences. It can be seen from Fig. 5 that the orthobaric density curves of the individual paraffins are similar in shape,

* Experiments published in the ETH thesis of H. Wild, Zurich, 1945.

and can be made to coincide by a suitable displacement. This is not the case with the cyclic hydrocarbons (Fig. 6). The orthobaric density curves of the higher members are so steep on the liquid side that the individual curves intersect*, and this is the reason that the densities (at a certain arbitrarily chosen temperature) of the homologous series of cyclic compounds reach a maxi-

* The points of intersection of the curves are not shown in Fig. 6.

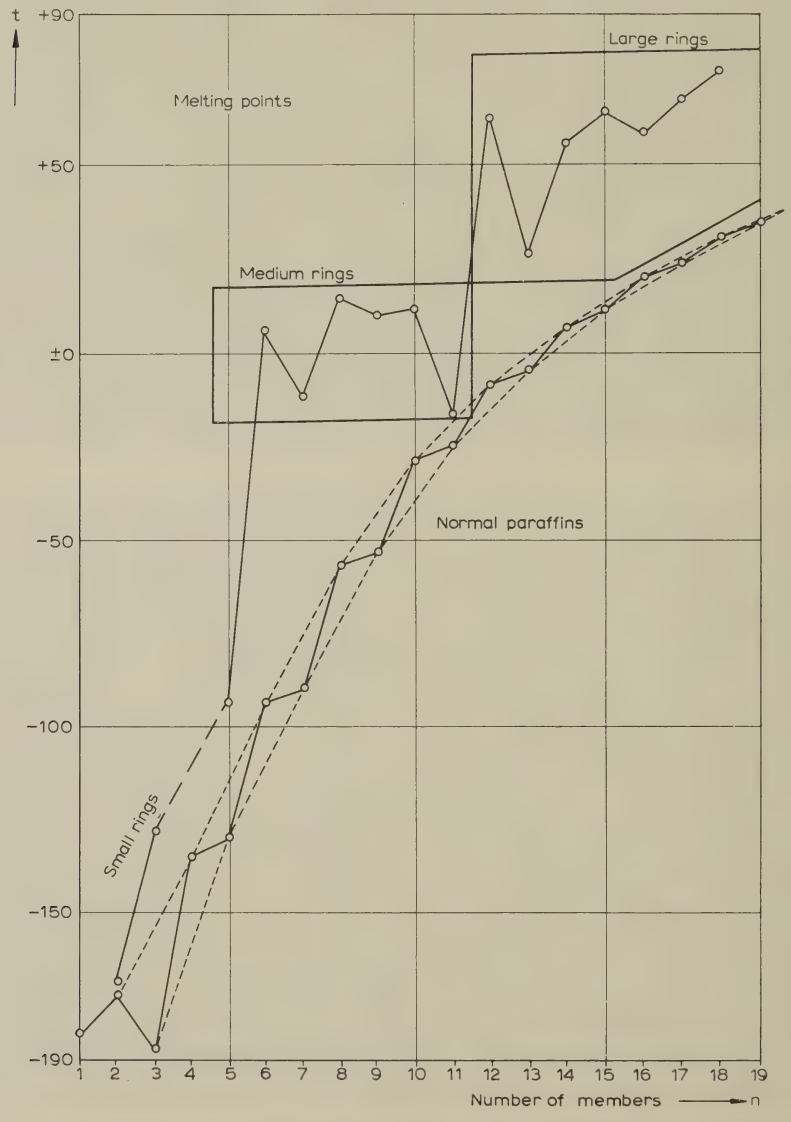


Fig. 4. Melting-point curves of normal paraffins and cycloparaffins (polymethylenes).

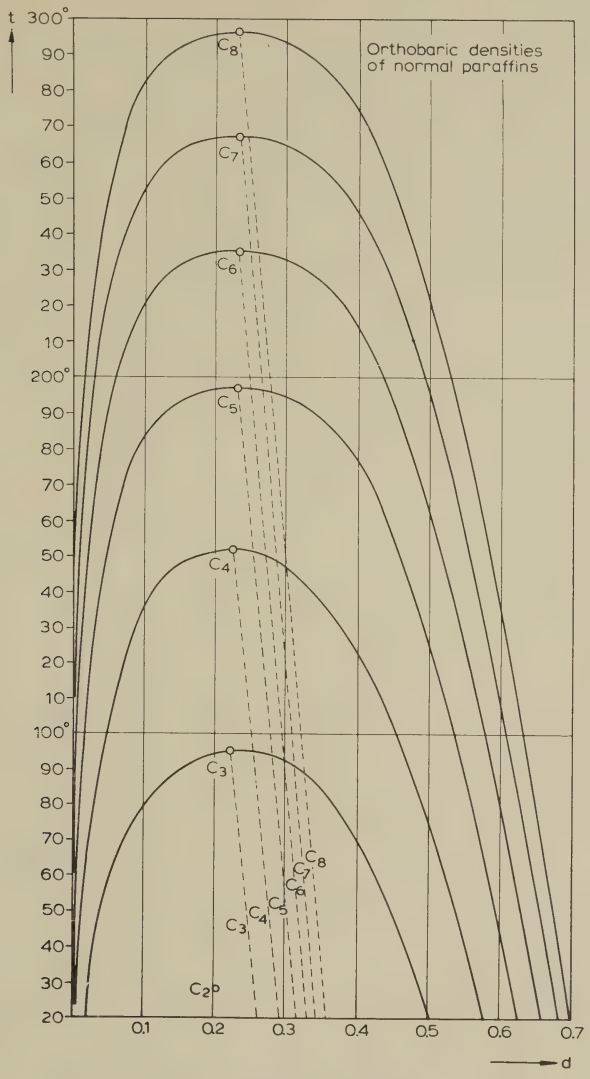


Fig. 5. Orthobaric densities of normal paraffins.

mum with a certain ring system which depends on the temperature selected. In the cycloparaffin series, for example, the maximum density at $-50°$ is shown by cyclodecane, and that at 20° by cyclotetradecane. Only at about 150° does this maximum completely disappear, and the density curves for a given temperature above this value follow a similar course (i.e. they rise continuously with increasing molecular size) to that observed at lower temperatures for the aliphatic compounds.

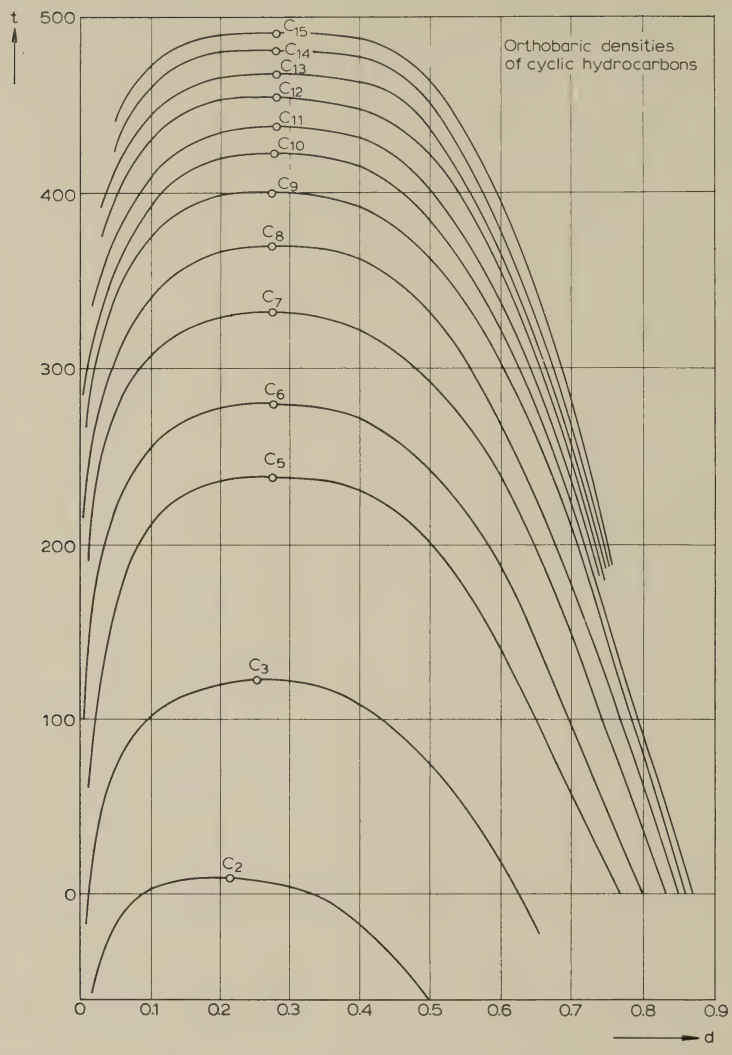
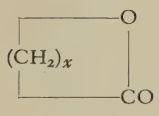


Fig. 6. Orthobaric densities of cycloparaffins.

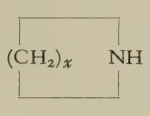
The homologous series of cyclic ketones provides a typical example of the dependence of physiological properties on details of the molecular structure. Whereas the familiar mixed odour, between bitter almond, caraway and peppermint, occurs with the 5- to 8-membered ring ketones, the 10- to 12-membered compounds have a characteristic camphor odour. The musk odour is found with the 14- to 18-membered ketones, the optimum, in the case of the unbranched and saturated cyclic ketones, occurring with cyclopentade-

none. Numerous multimembered heterocyclic compounds prepared subsequently, such as lactones[13], esters and imines, also show a musklike odour. The optima in this series occur roughly with the compound which contains 15 carbon atoms in the ring in addition to the hetero-atom.

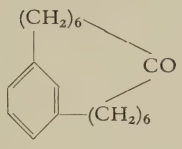
The first multimembered heterocyclic compounds were prepared from cyclic ketones by conventional methods of ring expansion. Thus, multimembered ketones gave the corresponding lactones (XII) when treated with Caro's acid, whilst the cyclic imines (XIII) could be prepared from the ketoximes by a Beckmann rearrangement, followed by reduction of the isoxime carbonyl to a methylene group.



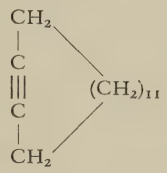
(XII)



(XIII)



(XIV)



(XV)

It is a well-known fact that a small ring can be fused to the benzene ring only in the *ortho*-position. It was to be expected, however, that sufficiently large rings could also be closed on the *meta*- and *para*-positions. This was in fact confirmed. As an example, we mention the first experimentally realized case, namely 6,6′-(*m*-phenylene)-dihexyl ketone (XIV).

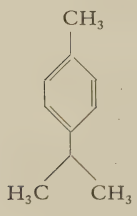
Experience has also shown that a normal triple bond cannot exist in a small ring, since the triply bonded carbon atoms and the adjacent carbons lie in a straight line. An examination of the model shows that a triple bond should be possible in a sufficiently large ring. This assumption was experimentally confirmed by the preparation of cyclopentadecyne (XV).

Ziegler[14] later achieved a considerable improvement in the yields of multimembered cyclic ketones, by appropriate use of the principle (first reported by Paul Ruggli) of ring formation in a very dilute solution. Whereas this method permits of at least a ten-fold increase in the yields of the 15- to 17-membered cyclic ketones, the yield of cyclodecanone still remains at a minimum of a few tenths of a per cent. Multimembered heterocyclic rings[15] have also been prepared by means of the principle of « infinite dilution ». We may recall here the first experimental achievement of the practically quantitative lactonisation[16] of 15-hydroxy-1-pentadecanoic acid. The resulting lactone

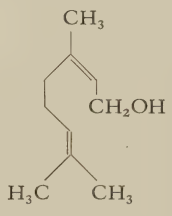
(XII, $x = 14$) was the same as that which had already been prepared by the action of Caro's acid on cyclopentadecanone, and which finds practical application as one of the best musk perfumes (« Exaltolid »). Cyclic imines of the type XIII have also been prepared in very dilute solution by cyclization of ω-bromoalkylamines[17].

Higher terpene compounds

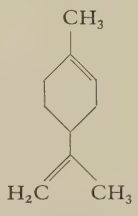
A second field on which I have to report is that of the higher terpenes. My remarks are, in some respects, an extension in higher molecular spheres of the lecture delivered here in 1910 by Otto Wallach on *monoterpenes*. The structural similarity of almost all monoterpenes was at that time best expressed by regarding *p*-cymene as the aromatic parent hydrocarbon of this class. To illustrate the close relationships we show here the formula of *p*-cymene together with those of an aliphatic, a monocyclic and a bicyclic monoterpene.



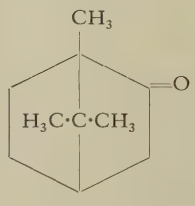
p-Cymene



Nerol

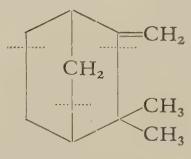


Limonene

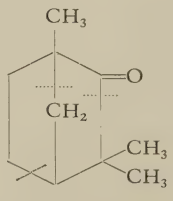


Camphor

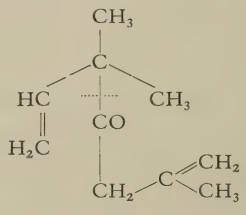
Even 35 years ago there were known compounds such as camphene and fenchone which, according to their properties, are monoterpenes, but which cannot be derived from *p*-cymene. Other monoterpenes of similar type were subsequently discovered in nature, such as artemisia ketone.



Camphene



Fenchone

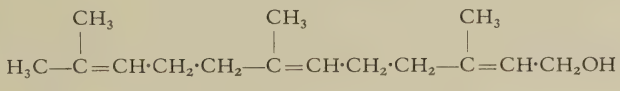


Artemisia ketone

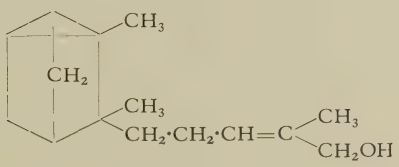
However, the carbon skeletons of this group of monoterpenes have one characteristic in common with that of *p*-cymene: they are built up of two isoprene

units*. The following is therefore proposed as a definition embracing all monoterpenes: Monoterpenes are compounds whose carbon skeleton is built up of two isoprene units.

In essential oils, the monoterpenes are frequently accompanied by compounds containing 15 carbon atoms in the molecule and closely resembling the monoterpenes in their properties. The term *sesquiterpenes* was adopted for these compounds. Prior to 1920 the constitutions of two sesquiterpene compounds had been elucidated: the aliphatic farnesol[18] and the bicyclic α-santalol[19].



Farnesol



α-Santalol

Diterpenes had no place in the system of organic chemistry in 1920, nor did the natural compounds with 30 carbon atoms, whose properties no longer resembled those of the mono- and sesquiterpenes but which were nevertheless occasionally referred to as *triterpenes*.

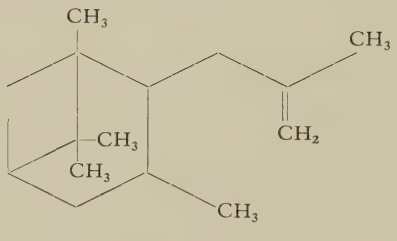
In 1920 we started work on a broad basis on sesquiterpenes, diterpenes and subsequently also on triterpenes, i.e. on compounds which may be grouped under the term « higher terpenes » or « polyterpenes ». The consistent application of a simple working hypothesis and a suitable method granted an insight into the structure of the carbon skeleton, which rapidly led to a systematization of the higher terpene compounds. The working hypothesis of that time, which is nowadays known as the *isoprene rule*, was based on the tentative assumption that the carbon skeleton of the higher terpenes is built up of isoprene units.

In view of the very large number of naturally occurring higher terpene compounds, and considering their very complex structures, it was not to be expected that the usual methods of systematic degradation would lead within a reasonable interval of time to a far-reaching conclusion regarding the validity

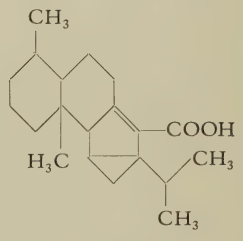
* Indicated in the formulae by dotted lines (...).

of the isoprene rule. On the other hand, it seemed to us that dehydrogenation would probably provide a more rapid method of achieving this end. This could only be successful if a large number of higher terpenes did in fact contain hydroaromatic ring systems and could be converted, on dehydrogenation, into the polycyclic aromatic parent hydrocarbons – homologues of naphthalene, phenanthrene, chrysene, picene – since it was to be expected that the constitutions of the latter could be more rapidly elucidated, and that they could be more readily synthesized than the natural hydroaromatic compounds. It was presumed that different natural products containing the same carbon skeleton, but differing from one another in other details (for instance, double bonds and functional groups) would yield the same aromatic parent substance. We also hoped that many higher terpenes which, instead of hydrogenated benzene rings, contain other alicyclic ring systems, which in turn may have aliphatic side-chains, so that relationships similar to that of nerol, limonene, camphor or α-santalol might be expected.

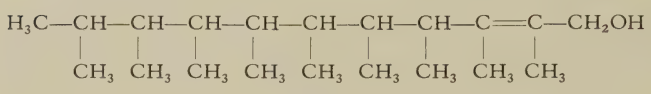
We may summarize the results of our experimental work by stating that the chosen way of investigation proved very fruitful. Moreover, a glance at some of the formulae proposed prior to 1921 for higher terpene compounds, (subsequently shown to be incorrect) also illustrates the usefulness of the chosen hypothesis as a guide for a rapid advance in this large and formerly confused field. These are the formulae of the sesquiterpene caryophyllene[20] and of the diterpenes phytol[21] and abietic acid[22], which do not follow the isoprene rule:



Caryophyllene



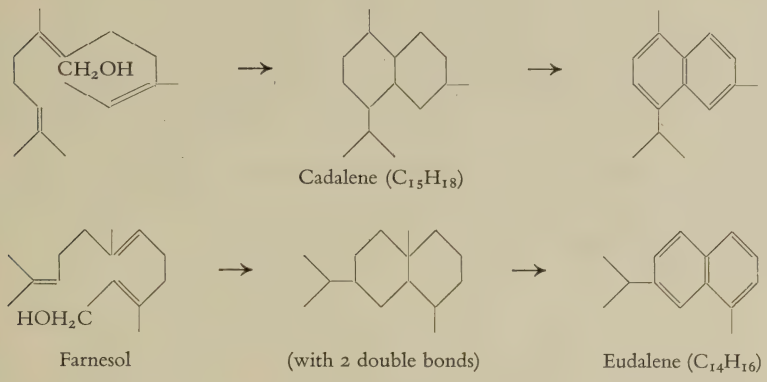
Abietic acid



Phytol

We shall now review some typical examples from the chemistry of higher terpene compounds. A discussion restricted mainly to the carbon skeletons will be sufficient to indicate the general traits of the mutual relationships of these compounds.

A number of bicyclic *sesquiterpenes* gave a naphthalene hydrocarbon $C_{15}H_{18}$ on dehydrogenation[23], whereas others gave the parent hydrocarbon $C_{14}H_{16}$. These observations were explained by the additional assumption that the carbon skeletons of these two subgroups of bicyclic sesquiterpenes are derived from farnesol by two formally different modes of cyclization.[24] It was actually the loss of one carbon atom in the formation of the dehydrogenation product $C_{14}H_{16}$ from the starting material containing 15 carbon atoms, which encouraged us to the hypothesis which is formulated below:

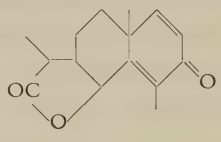


The structural formulae deduced for the two dehydrogenation products, cadalene ($C_{15}H_{18}$) and eudalene ($C_{14}H_{16}$), could be confirmed by synthesis of these hydrocarbons.

The cyclisation of farnesol into a hydrogenated naphthalene derivative of the cadalene type could also be effected in the laboratory; furthermore, we were able to isolate the hypothetical monocyclic intermediate in this transformation and to identify it as the naturally occurring hydrocarbon bisabolene $C_{15}H_{24}$.

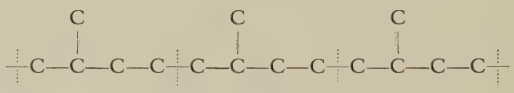
The positions of the double bonds and of the oxygen atoms in the sesquiterpene carbon skeletons elucidated in this manner, as well as the position of the methyl-group split off during the dehydrogenation, have been determined

by degradation methods, although in some cases only with considerable effort. The first sesquiterpene compound of the eudalene type in which the postulated position of the methyl-group split off during dehydrogenation could irrevocably be confirmed is santonin[25].

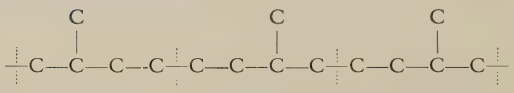


Santonin

Whereas the sesquiterpenes of the cadalene and eudalene type can be derived schematically from a regular isoprene chain, other sesquiterpenes have been discovered, which cannot be dealt with here, the formation of which could be explained by assuming an irregular condensation of isoprene units. These sesquiterpenes must be placed in an analogous class to the above-mentioned monoterpenes of irregular structure (e.g. fenchone).

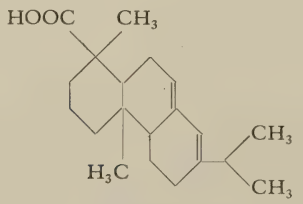


Regular isoprene chain

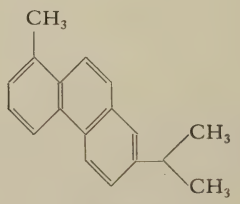


Example of an irregular isoprene chain

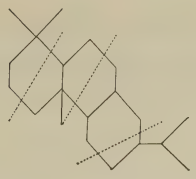
The first compound in the series of tricyclic *diterpenes* whose carbon skeleton was elucidated has by dehydrogenation and degradation an irregular structure consisting of four isoprene units[26]. This compound is abietic acid, which occurs in rosin, and by the dehydrogenation of which Vesterberg some time ago obtained the phenanthrene hydrocarbon retene.



Abietic acid

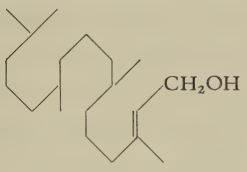


Retene

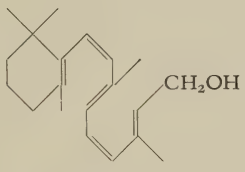


Irregular structure of the abietic acid skeleton, built up of 4 isoprene units

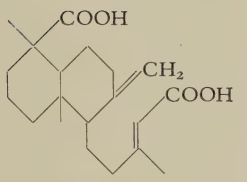
In contrast to abietic acid, the majority of diterpenes can be derived from a regular chain of 4 isoprene units. We mention here examples of an aliphatic, a monocyclic, and a bicyclic natural diterpene. The tricyclic compound isoagathic acid is an artefact which can be prepared by ring closure from agathic acid, a resin acid occurring in some copals[27].



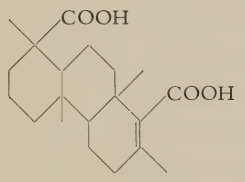
Phytol



Vitamin A



Agathic acid

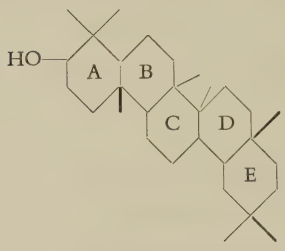


Isoagathic acid

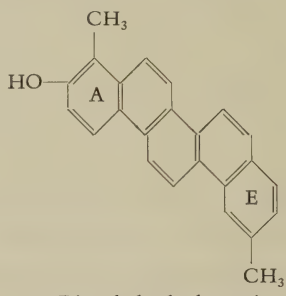
The formulae of two important natural products are shown above; these are phytol[28], which is the alcoholic constituent in chlorophyll, and vitamin A[29]. The elucidation of the constitution of these compounds, which are obtainable only in small quantities, would have met with exceptional difficulties without the guidance provided by the isoprene rule. In both cases the elucidation of the structure was facilitated by confirmation of the formula, deduced from the isoprene rule, by synthesis of either the natural product itself (in the case of phytol) or its perhydro derivative (in the case of vitamin A).

To demonstrate the complicated architecture in the *triterpene* field we will

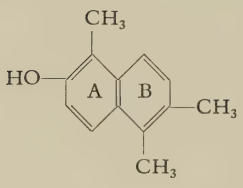
restrict our discussion to the carbon skeleton* of the pentacyclic sub-group of the β-amyrin type, which is widely distributed in nature.

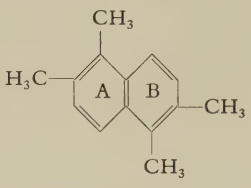


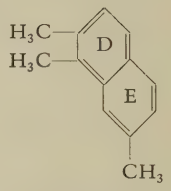
β-Amyrin skeleton



1,8-Dimethyl-2-hydroxypicene







Sapotalene

On the basis of the by synthesis elucidated dehydrogenation products, of which the four most important are shown here, there remain only three carbon atoms about which no information has been gained through dehydrogenation. These three carbon atoms are indicated by heavy lines in the above β-amyrin carbon skeleton. However, the degradation products of various triterpenes have directly or indirectly made it possible to localize these three side chains, at the positions shown. The position of the double bond was determined in a similar way. Degradation results have also yielded further information on practically all the ring carbon atoms.

The elucidation of the carbon skeleton of the other triterpene sub-groups, also depends on obtaining information about each individual carbon atom on the basis of reliable dehydrogenation and degradation results.

Although the *isoprene rule* has proved an extremely valuable guide in many cases–including the elucidation of the constitution of the carotenoids (i.e. tetraterpenes) by Karrer and Kuhn–it nevertheless can not be regarded as an

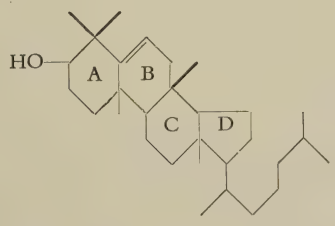
* Containing the hydroxyl group present at the same position in almost all natural triterpenes.

infallible law. This working hypothesis makes it possible to give precedence in experimental work to one or a few of the various carbon skeletons coming into consideration, and so to save a great deal of unnecessary work. Even if it is occasionally found, that the isoprene rule is not strictly valid for a given natural compound of a terpene type, this does not detract from its value as a working hypothesis. Experience has shown that there is no rule governing the architecture of natural compounds which is valid without exception, and which would enable us to dispense with the need to test its validity accurately for every new compound to be examined. This necessity remains, irrespective of whether the rule in question had in the past appeared to be applicable without exception, or whether exceptions had already been encountered.

Attempts may be made to interpret the isoprene rule, not only as a working hypothesis in the laboratory, but also as a structural principle employed by nature. The structural similarities of the higher terpenes raise the question as to whether these compounds may have been formed according to a uniform principle in nature[30]. At the present time, however, there is no point of reference which might lead to an interpretation of the mechanism of this biochemical process, which is so widely distributed in nature.

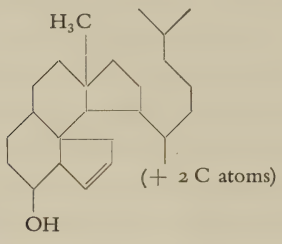
Male sex hormones

In addition to the terpene compounds proper, which are characterized by the presence of a number of carbon atoms divisible by 5, there exist also chemically related groups of compounds, including e.g. santene with 9 carbon atoms, the ionones with 13, and irone with 14; these may be referred to as terpenoids. Their carbon skeleton can be formally completed by addition of the missing 1–2 carbon atoms to give a basic structure that obeys the isoprene rule.

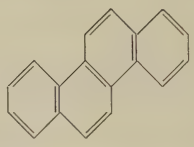


The present-day formula for cholesterol, supplemented by 3 methyl groups (—) to represent a hypothetical triterpene.

According to this view, cholesterol could be regarded as a triterpenoid[31]. On the basis of the incorrect formula which, during the years 1930–1932–at a time when we were engaged in interpreting the results of dehydrogenation of the triterpenes–was still generally accepted as representing the structure of cholesterol*, the formation of chrysene, obtained by Diels as a dehydrogenation product of steroids, could be explained only by assuming complex and unintelligible rearrangements.

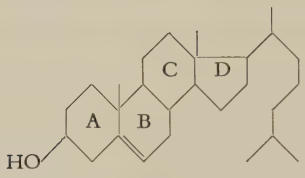


Cholesterol up to the beginning of 1932*

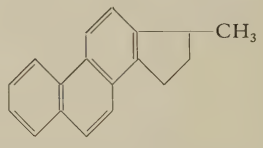


Chrysene

Consequently, dehydrogenation was temporarily discredited as a method of determining the carbon skeleton. Our results from the dehydrogenation of the triterpenes could be used for the determination of the carbon skeleton only on the assumption, unproved at that time, that the dehydrogenation of the steroids could be explained in a normal manner. The new formula for cholesterol, proposed and conclusively established in 1932–1933 by Bernal, Rosenheim, Wieland and Windaus, brought the desired change in the position. The formation of chrysene became readily understandable on the basis of enlargement of the 5-membered to the 6-membered ring (making use of the methyl-group).



Cholesterol**



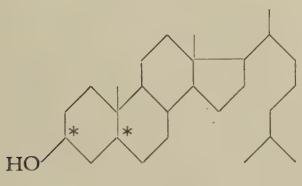
γ-Methylcyclopentenophenanthrene

This interpretation was confirmed by the fact that it explains the formation of γ-methylcyclopentenophenanthrene instead of chrysene when the dehy-

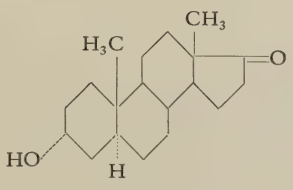
* This formula was advocated by Windaus and Wieland in their Nobel Lectures in 1928.
** Written in the manner which is presently used.

drogenation is carried out at moderately high temperatures. The migration of the methyl group is a result of the prior splitting off of the long side-chain.

At that time – from 1929 onwards – various chemists, particularly A. Butenandt, isolated the first sex hormones. The functional groups and, in the case of the female hormone oestrone, the structural formula – apart from stereochemistry – was rapidly established. In view of their tetracyclic structure, it seemed possible that the sex hormones of the oestrane and androstane type could be steroids in which the long sidechain of cholesterol had been split off. It was even conceivable the sex hormones might in the organism be formed from cholesterol by oxidative degradation of the long side chain, formally similar to the cleavage that occurs in dehydrogenation. Whether or not this assumption corresponded to reality, it was interesting to attempt the partial synthesis of a sex hormone in the laboratory by such a route. The most suitable example for this purpose was androsterone, isolated from male urine by Butenandt. The empirical formula of androsterone had not been accurately determined by analytical methods at that time (1932/1933) but if the above assumption regarding the relationship of the sex hormones to cholesterol were correct androsterone would have to be assigned the empirical formula $C_{19}H_{30}O_2$. There were four known stereoisomeric saturated sterols that could be used as starting materials for a partial synthesis of androsterone. In the general formula given here for these four sterols, the 2 carbon atoms involved in the stereoisomerism are indicated by asterisks. By oxidation of the acetates of the four stereoisomers, we were in fact able, during the period 1932–1934, to prepare the acetates of the expected four stereoisomeric hydroxy ketones $C_{19}H_{30}O_2$; the one obtained from epidihydrocholesterol was found to be identical with androsterone[32].



4 Stereoisomeric sterols

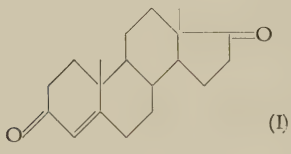


Androsterone

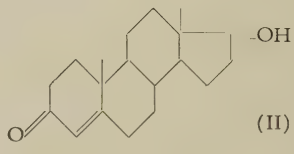
This conversion was not only the first synthesis of a sex hormone, but also the first complete structural elucidation of such a compound, and the first exact proof of the relationship between a sex hormone and a sterol – a relationship that agrees in the last stereochemical details. Afterwards such a relationship was also confirmed by other workers for the corpus luteum hormone.

Comparative physiological tests showed that androsterone must differ from the true male sex hormone occurring in the testicles, which had not been isolated in a pure form prior to 1935[34]. Even before the true testicle hormone had been isolated, we were able to gain some idea of its probable structure on the basis of the following considerations[33,36].

The method used for the partial synthesis of androsterone permitted the preparation of a series of compounds that were related chemically to androsterone and in part also exhibited male hormone activity. This proved that a series of androstane derivatives possess male hormone activity and it was therefore permissible to assume that the testicle hormone might also be related to androsterone. An indication of the possible position and the nature of the functional groups in the molecule of the testicle hormone was furnished by the observation, made in physiological laboratories, that the male hormone activity is destroyed when the testicle extract is treated with potassium permanganate or boiled with alkali, whereas androsterone (and the male hormone activity of concentrated urine) remains unchanged when subjected to such treatments. Since unsaturated ketones containing a double bond immediately adjacent to the keto group are known from experience to be sensitive to alkali, we considered one of the following two formulae for the testicle hormone[33]:



(I)



(II)

Testosterone

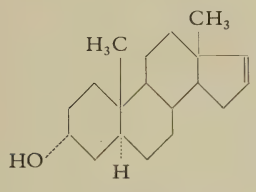
The second of these two formulae could be regarded as the more likely. It was known at the time that the reduction product of androsterone, androstanediol, has a greater hormone activity than androsterone itself. It was therefore to be assumed that the second hypothetical formula for the testicle hormone would represent the more active compound and would therefore be that preferred by nature.

These two compounds were prepared in 1935, starting from cholesterol[33,35,36]. At the same time, Laqueur's laboratory[34] reported the isolation of the testicle hormone from the testes of bulls. This hormone, called testosterone, proved to be identical with the synthetic unsaturated hydroxyketone

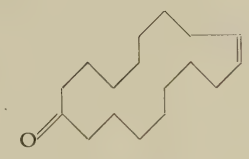
II, although the Dutch colleagues had at first indicated the wrong empirical formula $C_{19}H_{30}O_2$ which pointed to a stereoisomer of androsterone.

Of the more recent results obtained since 1939 in the steroid field we shall mention only one, which leads us back to a problem mentioned in the first part of this lecture.

In experiments carried out in our laboratory with the object of isolating steroids, and in particular sex hormones, of various animals, V. Prelog discovered 3α-androstenol in pig testicles. This unsaturated steroid alcohol exhibits the characteristic musk odour, which suggests a relationship between the molecular structure of this new musk perfume and that of civetone.



3α-Androstenol



Civetone

If the 3 bridges between the 4 rings in androstenol are imagined to be split, a doubly methylated 17-membered ring is obtained, in which the double bond and the oxygen atom occupy the same relative positions as in civetone.

1. W. H. Perkin, *J. Chem. Soc.*, (1929) 1347.
2. W. Markovnikov and A. Krestovnikov, *J. Russ. Chem. Phys.*, 12 (1881) 452; *Ann.*, 208 (1881) 347.
3. A. Freund, *Monatsh.*, 3 (1882) 625.
4. U. Sachse, *Z. Physik. Chem.*, 10 (1892) 203.
5. *Cf.* review by J. Böeseken, *Bull. Soc. Chim. France*, [5] 3 (1936) 1.
6. W. Hückel and H. Friedrich, *Ann.*, 451 (1926) 132.
7. L. Ruzicka, *Helv. Chim. Acta*, 9 (1926) 230 (submitted on January 26, 1924).
8. I am indebted to Ph. Chuit [*Helv. Chim. Acta*, 9 (1926) 264; cf. also later papers] for the preparation of the homologous series of the then largely unknown higher normal dicarboxylic acid.
9. Recently, Philip G. Stevens [*J. Am. Chem. Soc.*, 67 (1945) 907] detected the presence in the musk rat of 13-, 15-, 17- and 19-membered compounds, all of which could perhaps be derived from fatty acids containing from 14 to 20 carbon atoms.
10. L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, 9 (1926) 249, and subsequent papers.
11. L. Ruzicka and P. Schläpfer, *Helv. Chim. Acta*, 16 (1933) 162.
12. A. Müller, *Helv. Chim. Acta*, 16 (1933) 155.

13. Two multimembered lactones were detected by M. Kerschbaum, [*Ber.*, 60 (1927) 902] in two plant oils which possess a musk-like odour, namely musk seed oil and angelica root oil. According to experience gained to date, musk perfumes of vegetable origin are lactones, whilst those of animal origin are ketones.
14. K. Ziegler and R. Aurnhammer, *Ann.*, 513 (1934) 43.
15. The preparation by W. H. Carothers [*J. Am. Chem. Soc.*, 51 (1929) 2548; 55 (1933) 4714; 58 (1936) 654] of a large number of multimembered heterocyclic compounds (particularly lactones and esters) is undoubtedly also based on cyclization in a very dilute medium.
16. M. Stoll and A. Rouvé, *Helv. Chim. Acta*, 17 (1934) 1283.
17. L. Ruzicka, G. Salomon, and K. E. Meyer, *Helv. Chim. Acta*, 20 (1937) 109.
18. M. Kerschbaum, *Ber.*, 46 (1913) 1732.
19. F. W. Semmler, *Ber.*, 43 (1910) 1893.
20. W. Semmler and E. W. Mayer, *Ber.*, 44 (1911) 3657.
21. R. Willstätter, *Ann.*, 378 (1911) 81.
22. O. Aschan and A. I. Virtanen, *Ann.*, 424 (1921) 119, 150.
23. L. Ruzicka and J. Meyer, *Helv. Chim. Acta*, 4 (1921) 505; 5 (1922) 345.
24. L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, 5 (1922) 923.
25. L. Ruzicka and A. Capato, *Helv. Chim. Acta*, 17 (1934) 614.
26. L. Ruzicka, G. B. R. de Graaf, and H. J. Muller, *Helv. Chim. Acta*, 15 (1932) 1300.
27. L. Ruzicka and J. R. Hosking, *Helv. Chim. Acta*, 14 (1931) 203.
28. F. G. Fischer, *Ann.*, 464 (1928) 69; 475 (1929) 183.
29. P. Karrer et al., *Helv. Chim. Acta*, 14 (1931) 1431; 16 (1933) 625.
30. Added in 1965: Such a uniform general principle is defined in the «biogenetic isoprene rule». L. Ruzicka et al., *Experientia*, 9 (1953) 357; A. Eschenmoser et al., *Helv. Chim. Acta*, 38 (1955) 1890; L. Ruzicka, *Proc. Chem. Soc.*, (1959) 341, and *Pure Appl. Chem.*, (1963) 493.
31. The possibility that cholesterol might be derived from a hypothetical triterpene was one of my old cherished reveries. It was first put forward in discussion following a lecture of H. Wieland on bile acids before the Zurich Chemical Society in May 1923, and was subsequently published in the ETH thesis of my student E. A. Rudolph (Zurich, 1925). See also L. Ruzicka, *Experientia*, 9 (1953) 364. This old hypothesis has been confirmed by K. Bloch in his well-known work on the biogenesis of cholesterol.
32. L. Ruzicka, M. W. Goldberg, J. Meyer, H. Brüngger, and E. Eichenberger, *Helv. Chim. Acta*, 17 (1934) 1389.
33. L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, 18 (1935) 986.
34. K. David, E. Dingemanse, J. Freud, and E. Laqueur, *Z. Physiol. Chem.*, 233 (1935) 281.
35. L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, 18 (1935) 1264.
36. The first description of the procedure for the preparation of testosterone was given in a Swiss patent application from June 18, 1935 (which was the priority date for patents in many countries), and in a communication of my colleague A. Wettstein from September 10, 1935 in *Schweiz. Med. Wochschr.*, 65 (1935) 912.
    A. Butenandt and Hanisch, *Ber.*, 68 (1935) 1859, published in a preliminary note the preparation of testosterone using independently the same series of reaction steps.

Biography

Leopold Stephen Ružička* was born on September 13, 1887, in Vukovar, a small Croatian town on the Danube, somewhat east of its confluence with the Drava. His father, Stjepan Ružička, was a cooper; his mother's maiden name was Ljubica Sever. His great-grandparents included a Czech, from whom the name Ružička stems, an Upper Austrian and his wife from Wurtemberg, the other five being Croats. His ancestors were artisans or farmers, who had enjoyed at most a few years of schooling. After the early death of his father in 1891, he returned with his mother to her birthplace, Osijek, on the Drava somewhat west of its junction with the Danube. There he attended the primary school and the classical gymnasium where the Croatian language was used. He was a fairly good pupil in a general way, but really interested only in physics and mathematics. The other subjects, including the purely descriptive sciences, left him cold. There was no chemistry in the curriculum but, nevertheless, he decided to study this subject out of his interest in the composition of natural products.

He wanted to study at the Zurich Polytechnic Institute but found to his dismay that an entrance examination was required not only in chemistry but also in « descriptive geometry ». He decided to go instead to Germany, where anyone with a completed secondary school education was acceptable as a student at a University or Technical Institute without having to undergo additional entrance examinations. He chose the Technische Hochschule at Karlsruhe, where he began his chemical studies in 1906. This step proved to be decisive for his future. Only later did he discover that in Zurich the curriculum, including practical work, was organized on a very rigid basis; still in 1906 attendance at the lectures was or could be checked. In Karlsruhe, on the other hand, there was considerable freedom. He completed his laboratory courses in $1\frac{3}{4}$ years and then immediately started his doctoral work on ketenes with Professor Staudinger, who was, at 27, only $6\frac{1}{2}$ years older, There were few bureaucratic formalities; he had attended the prescribed

* The pronunciation can be best explained by the French transcription «Rougitchka».

lectures neither in chemical technology nor, unfortunately, in physical chemistry and physics.

After two years of research work Ružička was «Dipl. Ing», and two weeks later «Dr. Ing». Staudinger appointed him as his assistant, and they together entered the quite unexplored field of the active constituents – named by them pyrethrins – of Dalmatian insect powder, a plant product, toxic to insects and other coldblooded animals. They thus opened a new chapter of alicyclic chemistry, which was then as unfamiliar to Ružička as it was to Staudinger.

In October 1912 he followed Staudinger who became Willstätter's successor at the newly dubbed «Eidgenössische Technische Hochschule» (ETH, Swiss Federal Institute of Technology) at Zurich. In Switzerland he found not only a second homeland but also a peaceful and convivial environment that brought with it all the conditions for uninterrupted research. In 1917 he acquired Swiss citizenship.

In the previous year he had already started independent work and this decision initiated the most fruitful and happy decade of his life, when he could work at the laboratory bench from morning to night, on problems of his own choosing, with no teaching responsibilities, except one hour weekly from 1918 onward. During the years 1920–1924 he laid the fundaments of all his future work.

For the accomplishment of his Habilitation work (necessary to become a «Privatdozent») in 1916–1917 he was glad of the support of the oldest perfume manufacturers in the world, Haarman & Reimer, of Holzminden in Germany. The starting-point for their collaboration was the Tiemann formula for irone; the results were the total synthesis of fenchone and the extension and interpretation of the Wagner rearrangement (this term was then introduced by him). After his habilitation in 1918 the firm of Ciba, Basle, became interested in his work on the preparation of quinine-like compounds. With various co-workers, the first synthesis of β-collidine and of linalool, the partial synthesis of pinene, and a series of investigations in the monoterpene field were carried out.

In 1921, the Geneva perfume manufacturers Chuit, Naef & Firmenich, asked him to collaborate with them. By this time the investigations that were to lead to the elucidation of the constitutional formulas of the higher terpenes has already been started (2nd section of his Nobel Lecture). In the perfumery and sesquiterpene domain the total syntheses of nerolidol and farnesol were carried through. The structure of jasmone was established, Tiemann's irone formula corrected, and synthetic work in these fields undertaken. But by far

the most important fruits collected in the perfumery garden were the elucidations of the structures of the naturally occurring musk perfumes, civetone and muscone. Following these discoveries Ružička and his co-workers were able to prepare the whole series of alicyclic ketones with 9 to over 30 carbon atoms as ring members, compounds that had previously been believed to be incapable to existence (1st section of his Nobel Lecture).

Most of the years 1925–1926 he spent with his friends in Geneva. From October 1926 till 1929 he was Professor of Organic Chemistry at the University of Utrecht. Although he was very happy in Holland, he decided to accept the invitation of the ETH to return to Zurich. The main reason for this decision was the strength of the Swiss organic chemical industry, especially its pharmaceutical and perfumery branches, which required the skill and energy of a whole army of chemists with a thorough training in modern organic chemistry. This circumstance was not only a challenge to the teaching and research abilities of the professors; it also encouraged students to acquire the necessary understanding of the theories and methods to equip them for a career in these industries. The three-fold community of professors, students and industry was thus bound together by bonds of common interest.

In 1930, the Ciba renewed the contact with his laboratory. This association led in a few years to scientifically as well as industrially important successes in the field of the male sex hormones (3rd section of his Nobel Lecture). From 1937 the Rockefeller Foundation generously provided financial backing for the research on natural compounds, especially the triterpenes and steroids, free from any special conditions. With the two industries, there was thus formed a strong group of constant supporters of his research team which had grown much in the meantime.

Professor Ružička holds eight honorary doctorates (4 Science, 2 Medicine, 1 Natural Sciences, 1 Law) 7 prizes and medals, 24 honorary memberships of chemical, biochemical and other scientific societies, 18 honorary, ordinary and foreign memberships of scientific academies. The circle of his friends is very wide, not only geographically but also spiritually, including the Vatican City as well as Moscow. He feels that the honours which he has won should be distributed among the whole team of his co-workers, and that, to mention only one example, the laudation of his 1936 honorary Doctor diploma of Harvard (tercentenary celebration of the oldest USA university) should more realistically be read in the plural form «... to the team of chemists, daring in their attacks, brilliant in their methods, successful in their interpretations of the architecture of nature's baffling compounds», since every mem-

ber of the team helped to transform the youthful dreams of its oldest member into reality.

Ružička married Anna Hausmann in 1912, and Gertrud Acklin in 1951. He has no children, and lives in Zurich. His hobbies are old Dutch and Flemish paintings and alpine plants gardening.

Chemistry 1940

Prize not awarded.

Chemistry 1941

Prize not awarded.

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